

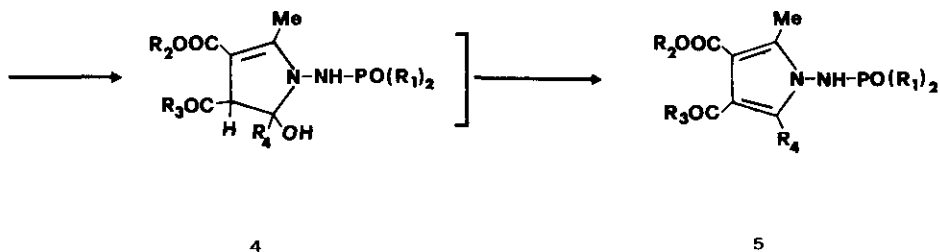
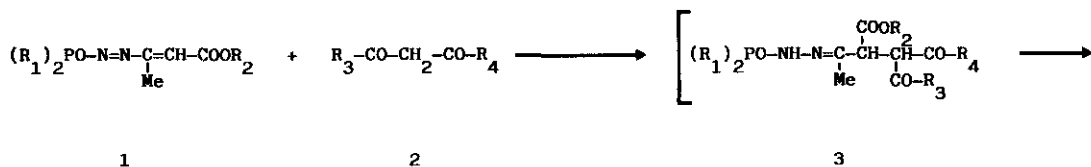
**EFFECT OF METAL IONS IN ORGANIC SYNTHESIS. XXXVI. ONE-POT SYNTHESIS OF NEW 3-CARBONYL- AND 3-CARBOXY-N-PHOSPHORUS-1-AMINOPYRROLES**

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**Abstract** - The one-pot synthesis of a lot of new 3-carbonyl-N-phosphorus-1-aminopyrroles and 3-carboxy-N-phosphorus-1-aminopyrroles by reaction of some N-phosphinic and N-phosphonic conjugated azoalkenes with  $\beta$ -diketones and  $\beta$ -ketoesters is reported. A different role played in these reactions by copper(II) chloride catalyst was also observed.

N-Phosphorus-1-aminopyrrole derivatives represent a class of unknown heterocyclic compounds, in spite of their potential interest in organic, biological, pharmaceutical, and phytopharmaceutical chemistry.<sup>1</sup> In view of these facts and considering our previous investigation on the chemical and physico-chemical properties of widely substituted 1-aminopyrroles,<sup>2</sup> we have attempted the direct synthesis of some 3-carbonyl-N-phosphinic- and 3-carbonyl-N-phosphonic-1-aminopyrroles (5a-e), as well as of some 3-carboxy-N-phosphinic- and 3-carboxy-N-phosphonic-1-aminopyrroles (5f-i) by reaction of N-phosphinic (1a-b) and N-phosphonic (1c-g) conjugated azoalkenes with  $\beta$ -diketones (2a-c) and  $\beta$ -ketoesters (2d-f).

Very likely, the reaction proceeds via preliminary formation of the 1,4-adduct (3) producing 2-hydroxy-4-pyrroline intermediate (4), due to an internal cyclization. The loss of a water molecule from this latter intermediate affords pyrrole derivative, according to our previous finding on this matter.<sup>2,3</sup> In some cases (5a, 5b and 5f), the catalytic role by copper(II) chloride dihydrate was clearly revealed because faster and cleaner reactions were observed in contrast to those in the absence of this inorganic salt. In other cases, no advantage (5d, 5g and 5h) or even worse (5c, 5e and 5i) complicated reaction mixtures were obtained in connection with the presence of copper(II) ions in the reaction media. For these reasons, the reactions were carried out in three different reaction conditions, as specified in experimental section and in Table. The reactions smoothly occur without complicated work-up procedures and do not require expensive or less readily available reagents. The yields of the reaction products may be considered rather good also bearing in mind the fact that N-phosphorus-1-aminopyrrole derivatives cannot be easily prepared by other methods.<sup>1</sup>



1	R <sub>1</sub>	R <sub>2</sub>	2	R <sub>3</sub>	R <sub>4</sub>
a	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	a	CH <sub>3</sub>	CH <sub>3</sub>
b	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	b	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
c	OC <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	c	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
d	OC <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	d	OCH <sub>3</sub>	CH <sub>3</sub>
e	OC <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	e	OC <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
f	OC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> CH <sub>3</sub>	f	OCH <sub>2</sub> CH <sub>3</sub>	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
g	OC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>			

#### EXPERIMENTAL

Mps were determined in capillary tubes with a Buchi apparatus, and are uncorrected. The products often decompose at melting point. Ir spectra were obtained in Nujol mull with a Perkin-Elmer 298 spectrophotometer, and significant  $\nu$  values are expressed in  $cm^{-1}$ . <sup>1</sup>H-Nmr spectra at 60 MHz were recorded on a Varian EM-360L spectrometer in DMSO-d<sub>6</sub> using TMS as internal standard. Chemical shifts ( $\delta$ ) are reported in ppm and coupling constants (J) in Hz. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; D<sub>2</sub>O ex, D<sub>2</sub>O exchange. Merck silica gel 60F<sub>254</sub> plates were employed for analytical thin layer chromatography (tlc), Merck silica gel PF<sub>254</sub> plates for preparative TLC, and silica gel Kieselgel 60 (0.063-0.200 mm) for column chromatography.  $\beta$ -Diketones (2a-c),  $\beta$ -ketoesters (2d-f), and copper(II) chloride dihydrate catalyst were commercial materials and were used without further

Table - Method, time, yield, melting point, and spectral data of N-phosphorus-l-aminopyrroles 5.

Product <sup>a</sup>	Reagents	Method	Reaction time (h)	Yield <sup>b</sup> (%)	Mp (°C) <sup>c</sup>	Ir (nujol) <sup>1</sup> H-nmr (DMSO-d <sub>6</sub> /TMS <sub>int</sub> ) ● cm <sup>-1</sup> δ ppm
5	1    2					
5a	1b   2b	A	60	48	148-150	3425, 3065 0.70 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> ), 2.00 (s, 3H, CH <sub>3</sub> ), 2.42 (s, 1690, 1645 3H, COCH <sub>3</sub> ), 3.77 (q, 2H, OCH <sub>2</sub> CH <sub>3</sub> ), 7.37-8.13 (m, 1595, 1230 15H, Ar), 9.45 (d, <sup>2</sup> J <sub>PH</sub> =22 Hz, 1H, NH, D <sub>2</sub> O ex) 3390, 3165 0.70-1.30 (m, 6H, OCH <sub>2</sub> CH <sub>3</sub> ), 2.60 (s, 3H, CH <sub>3</sub> ) 1700, 1600 3.37 (s, 3H, OCH <sub>3</sub> ), 3.23-3.80 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ) 1660, 1255 7.13-7.80 (m, 10H, Ar), 9.17 (d, <sup>2</sup> J <sub>PH</sub> =31 Hz, 1H, 970 NH, D <sub>2</sub> O ex)
5b	1c   2c	A	12	60	171-174	
5c	1d   2b	C	3	65	117-119	3380, 3110 1.00-1.53 (m, 6H, OCH <sub>2</sub> CH <sub>3</sub> ), 2.20 (s, 3H, CH <sub>3</sub> ) 1695, 1645 2.52 (s, 3H, COCH <sub>3</sub> ), 3.83-4.43 (m, 4H, OCH <sub>2</sub> CH <sub>3</sub> ) 1595, 1230 4.78 (s, 2H, OCH <sub>2</sub> Ph), 6.90-7.93 (m, 10H, Ar) 975 9.09 (d, <sup>2</sup> J <sub>PH</sub> =29 Hz, 1H, NH, D <sub>2</sub> O ex)
5d	1e   2a	B	1	50	123-125	3430, 3180 2.18 (s, 3H, CH <sub>3</sub> ), 2.32 (s, 6H, 2CH <sub>3</sub> ), 3.77 (s, 1700, 1660 3H, OCH <sub>3</sub> ), 7.10-7.73 (m, 10H, Ar), 10.04 (d, 1590, 1290 <sup>2</sup> J <sub>PH</sub> =31 Hz, 1H, NH, D <sub>2</sub> O ex) 945
5e	1g   2a	C	2	60	133-136	3380, 3090 2.30 (s, 3H, CH <sub>3</sub> ), 2.40 (s, 3H, CH <sub>3</sub> ), 2.45 (s, 3H, 1700, 1675 CH <sub>3</sub> ), 5.43 (s, 2H, OCH <sub>2</sub> Ph), 7.28-7.88 (m, 10H, Ar) 1590, 1270 10.20 (d, <sup>2</sup> J <sub>PH</sub> =32 Hz, 1H, NH, D <sub>2</sub> O ex) 970

Table (continued)

5f	1a	2f	A	20	55	208-210	3430, 3080	1.05 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> ), 2.65 (s, 3H, CH <sub>3</sub> ), 3.75 (s, 1715, 1605 3H, OCH <sub>3</sub> ), 4.05 (q, 2H, OCH <sub>2</sub> CH <sub>3</sub> ), 7.87-8.33 (m, 1460, 1240 14H, Ar), 9.68 (d, <sup>2</sup> J <sub>PH</sub> =25 Hz, 1H, NH, D <sub>2</sub> O ex)
5g	1d	2f	B	2	64	181-184	3390, 3130	0.78-1.32 (m, 9H, OCH <sub>2</sub> CH <sub>3</sub> ), 2.53 (s, 3H, CH <sub>3</sub> ) 1705, 1600 3.32-4.18 (m, 6H, OCH <sub>2</sub> CH <sub>3</sub> ), 5.28 (s, 2H, OCH <sub>2</sub> Ph) 1230, 975 7.47 (s, 5H, Ph), 7.77 (d, 2H, J=9 Hz, Ar), 8.38 (d, 2H, J=9 Hz, Ar), 9.34 (d, <sup>2</sup> J <sub>PH</sub> =31 Hz, 1H, NH, D <sub>2</sub> O ex)
5h	1e	2e	B	1	50	82-84	3405, 3120	1.07 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> ), 2.37 (s, 3H, CH <sub>3</sub> ), 3.75 (s, 1710, 1590 3H, OCH <sub>3</sub> ), 4.08 (q, 2H, OCH <sub>2</sub> CH <sub>3</sub> ), 6.67-7.63 (m, 1215, 960 15H, Ar), 10.12 (d, <sup>2</sup> J <sub>PH</sub> =34 Hz, 1H, NH, D <sub>2</sub> O ex)
5i	1f	2d	C	3	45	90-94	3400, 3100	1.23 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> ), 2.27 (s, 6H, 2CH <sub>3</sub> ), 3.73 1705, 1590 (s, 3H, OCH <sub>3</sub> ), 4.20 (q, 2H, OCH <sub>2</sub> CH <sub>3</sub> ), 7.13-7.73 1230, 965 (m, 10H, Ar), 10.05 (d, <sup>2</sup> J <sub>PH</sub> =32 Hz, 1H, NH, D <sub>2</sub> O ex)

<sup>a</sup>All the compounds showed satisfactory elemental analysis: C<sub>+0.35</sub>, H<sub>+0.30</sub>, N<sub>+0.30</sub>.

<sup>b</sup>Yield of pure isolated product.

<sup>c</sup>Melting points occur with decomposition.

purification.

**N-Phosphinic and N-phosphonic azoalkenes 1.** These products were prepared as previously reported.<sup>4</sup>

**3-Carbonyl-N-phosphorus-1-aminopyrroles and 3-carboxy-N-phosphorus-1-aminopyrroles 5 - general procedure:**  $\beta$ -diketone (2a-c) or  $\beta$ -ketoester (2d-f) (1 mmol) was added to a solution of N-phosphinic (1a-b) or N-phosphonic azoalkene (1c-g) (1 mmol) dissolved in tetrahydrofuran (2 ml). For the synthesis of 5a, 5b and 5f copper(II) chloride dihydrate (0.1 mmol) was added to the solution and the mixture was stirred at room temperature (method A), while the formation of 5d, 5g and 5h proceeds well also in absence of the inorganic salt as catalyst (method B). For the preparation of 5c, 5e and 5i the mixture was heated under reflux without copper(II) chloride (method C). The reaction was monitored by tlc on silica gel until azoalkene 1 disappeared. Tetrahydrofuran was removed under reduced pressure and the product 5 was isolated by chromatography on a silica gel column (elution with methylene chloride-ethyl acetate mixtures, gradually increasing the amount of ethyl acetate from 100/0 up to 50/50 (v/v) ratio). Further purification of the product 5 may be obtained by recrystallization from methylene chloride-pentane.

#### ACKNOWLEDGEMENT

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