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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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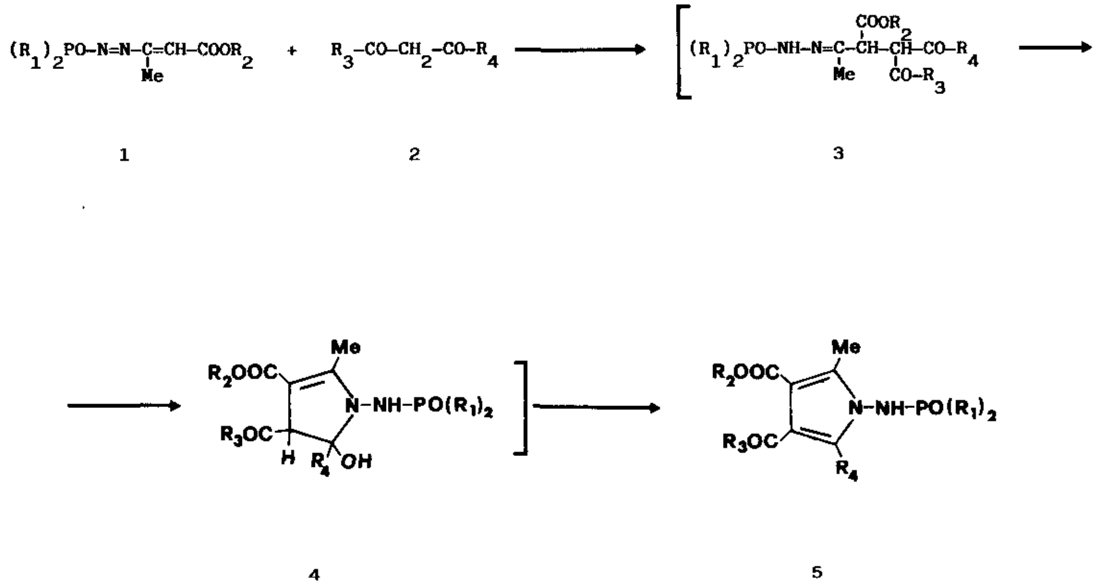
Abstract - The one-pot synthesis of a lot of new 3-carbonyl-N-phosphorus-1-aminopyrroles and 3-carboxy-N-phosphorus-1-aminopyrroles by reaction of some N-phosphinic and N-phosphonic conjugated azoalkenes with ß-diketones and ß-ketoesters is reported. A different role played in these reactions by copper(II) 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.[1] In view of these facts and considering our previous investigation on the chemical and physico-chemical properties of widely substituted 1-aminopyrroles,[2] 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 ß-diketones (**2a–c**) and ß-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.[2,3] 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.[1]



1	R_1	R_2	2	R_3	R_4
a	C_6H_5	CH_3	a	CH_3	CH_3
b	C_6H_5	C_2H_5	b	C_6H_5	CH_3
c	OC_2H_5	CH_3	c	C_6H_5	C_6H_5
d	OC_2H_5	$CH_2C_6H_5$	d	OCH_3	CH_3
e	OC_6H_5	CH_3	e	OC_2H_5	C_6H_5
f	OC_6H_5	CH_2CH_3	f	OCH_2CH_3	p-$NO_2C_6H_4$
g	OC_6H_5	$CH_2C_6H_5$			

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 significative ν values are expressed in cm^{-1}. ^1H-Nmr spectra at 60 MHz were recorded on a Varian EM-360L spectrometer in DMSO-d_6 using TMS as internal standard. Chemical shifts (δ) 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_2O ex, D_2O exchange. Merck silica gel $60F_{254}$ plates were employed for analytical thin layer chromatography (tlc), Merck silica gel PF_{254} plates for preparative tlc, and silica gel Kieselgel 60 (0.063–0.200 mm) for column chromatography. ß-Diketones (**2a–c**), ß-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-1-aminopyrroles **5.**

Product[a]	Reagents		Method	Reaction	Yield[b]	Mp (°C)[c]	Ir (nujol)	^{1}H-nmr (DMSO-d_6/TMS$_{int}$)
5	**1**	**2**		time (h)	(%)		● cm^{-1}	δ ppm
5a	**1b**	**2b**	A	60	48	148–150	3425, 3065 1690, 1645 1595, 1230	0.70 (t, 3H, $OCH_2\underline{CH_3}$), 2.00 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 3.77 (q, 2H, $O\underline{CH_2}CH_3$), 7.37–8.13 (m, 15H, Ar), 9.45 (d, $^2J_{PH}$=22 Hz, 1H, NH, D_2O ex)
5b	**1c**	**2c**	A	12	60	171–174	3390, 3165 1700, 1600 1660, 1255 970	0.70–1.30 (m, 6H, $OCH_2\underline{CH_3}$), 2.60 (s, 3H, CH_3) 3.37 (s, 3H, OCH_3), 3.23–3.80 (m, 4H, $O\underline{CH_2}CH_3$) 7.13–7.80 (m, 10H, Ar), 9.17 (d, $^2J_{PH}$=31 Hz, 1H, NH, D_2O ex)
5c	**1d**	**2b**	C	3	65	117–119	3380, 3110 1695, 1645 1595, 1230 975	1.00–1.53 (m, 6H, $OCH_2\underline{CH_3}$), 2.20 (s, 3H, CH_3) 2.52 (s, 3H, $COCH_3$), 3.83–4.43 m, 4H, $O\underline{CH_2}CH_3$) 4.78 (s, 2H, $O\underline{CH_2}Ph$), 6.90–7.93 (m, 10H, Ar) 9.09 (d, $^2J_{PH}$=29 Hz, 1H, NH, D_2O ex)
5d	**1e**	**2a**	B	1	50	123–125	3430, 3180 1700, 1660 1590, 1290 945	2.18 (s, 3H, CH_3), 2.32 (s, 6H, $2CH_3$), 3.77 (s, 3H, OCH_3), 7.10–7.73 (m, 10H, Ar), 10.04 (d, $^2J_{PH}$=31 Hz, 1H, NH, D_2O ex)
5e	**1g**	**2a**	C	2	60	133–136	3380, 3090 1700, 1675 1590, 1270 970	2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.43 (s, 2H, $O\underline{CH_2}Ph$), 7.28–7.88 (m, 10H, Ar) 10.20 (d, $^2J_{PH}$=32 Hz, 1H, NH, D_2O ex)

Table (continued)

5f	**1a**	**2f**	A	20	55	208-210	3430, 3080 1715, 1605 1460, 1240	1.05 (t, 3H, $OCH_2\underline{CH_3}$), 2.65 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.05 (q, 2H, $O\underline{CH_2}CH_3$), 7.87-8.33 (m, 14H, Ar), 9.68 (d, $^2J_{PH}$=25 Hz, 1H, NH, D_2O ex)
5g	**1d**	**2f**	B	2	64	181-184	3390, 3130 1705, 1600 1230, 975	0.78-1.32 (m, 9H, $OCH_2\underline{CH_3}$), 2.53 (s, 3H, CH_3) 3.32-4.18 (m, 6H, $O\underline{CH_2}CH_3$), 5.28 (s, 2H, $O\underline{CH_2}Ph$) 7.47 (s, 5H, Ph), 7.77 (d, 2H, J=9 Hz, Ar), 8.38 (d, 2H, J=9 Hz, Ar), 9.34 (d, $^2J_{PH}$=31 Hz, 1H, NH, D_2O ex)
5h	**1e**	**2e**	B	1	50	82-84	3405, 3120 1710, 1590 1215, 960	1.07 (t, 3H, $OCH_2\underline{CH_3}$), 2.37 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.08 (q, 2H, $O\underline{CH_2}CH_3$), 6.67-7.63 (m, 15H, Ar), 10.12 (d, $^2J_{PH}$=34 Hz, 1H, NH, D_2O ex)
5i	**1f**	**2d**	C	3	45	90-94	3400, 3100 1705, 1590 1230, 965	1.23 (t, 3H, $OCH_2\underline{CH_3}$), 2.27 (s, 6H, $2CH_3$), 3.73 (s, 3H, OCH_3), 4.20 (q, 2H, $O\underline{CH_2}CH_3$), 7.13-7.73 (m, 10H, Ar), 10.05 (d, $^2J_{PH}$=32 Hz, 1H, NH, D_2O ex)

[a] All the compounds showed satisfactory elemental analysis: C±0.35, H±0.30, N±0.30.

[b] Yield of pure isolated product.

[c] Melting points occur with decomposition.

purification.

N-Phosphinic and N-phosphonic azoalkenes 1. These products were prepared as previously reported.[4]

3-Carbonyl-N-phosphorus-1-aminopyrroles and 3-carboxy-N-phosphorus-1-aminopyrroles 5 – general procedure: ß-diketone (**2a–c**) or ß-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.

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