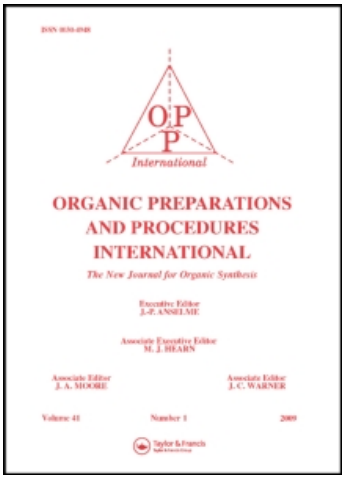

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EFFECT OF METAL IONS IN ORGANIC SYNTHESIS. PART XXVIII
SYNTHESIS OF NEW 1-AROYLAMINO-3-AMINOCARBONYLPYRROLES

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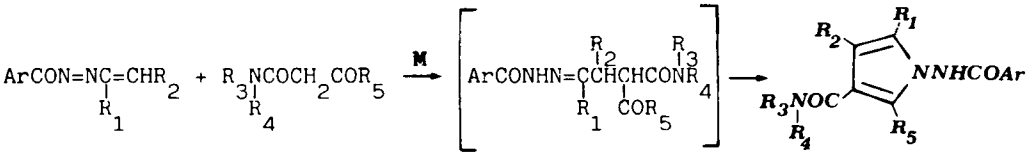
Some years ago we undertook the one-pot synthesis of new and interesting 1-aminopyrrole derivatives by reaction of azoalkenes with compounds containing activated methylene groups.[1-7] These reactions were frequently shown to be catalyzed by metal ions, particularly by copper(II) chloride. These 1-aminopyrrole derivatives are not easily prepared by other methods.[8] In view of these findings, the spectroscopic properties,[9] the X-ray crystal structures,[2,10] and the biological activity of some of these compounds have been studied. In order to generalize the present synthetic



1 **2** **3** **4**

M = $CuCl_2.2H_2O$

a) Ar = C_6H_5, R_1 = Me, R_2 = CO_2Me R_3 = H, R_4 = H, R_5 = Me

b) Ar = C_6H_5, R_1 = Me, R_2 = CO_2Et R_3 = Et, R_4 = Et, R_5 = Me

c) Ar = 3-ClC_6H_4, R_1 = Me, R_2 = CO_2Me R_3 = H, R_4 = C_6H_5, R_5 = Me

d) Ar = 3-ClC_6H_4, R_1 = Me, R_2 = CO_2Et R_3 = H, R_4 = 4-ClC_6H_4, R_5 = Me

e) Ar = 3-$CH_3C_6H_4$, R_1 = Me, R_2 = CO_2Me R_3 = H, R_4 = 4-$CH_3OC_6H_4$, R_5 = Me

f) Ar = $C_6H_5CH_2$, R_1 = Me, R_2 = CO_2Me R_3 = H, R_4 = C_6H_5, R_5 = C_6H_5

g) Ar = $C_6H_5CH_2$, R_1 = Me, R_2 = CO_2Et

methodology, we have devised a one-pot synthesis of some new 1-aroylamino-3-aminocarbonylpyrroles (**4**) by the reaction of aroylazoalkenes (**1**) with ß-ketoamides (**2**) under copper(II) chloride dihydrate catalysis. Under analogous experimental conditions, in the absence of the copper(II) salt, different and/or slower reactions, as well as mixtures with several by-products, were observed.

Table 1. Preparation of 1-Aroylamino-3-aminocarbonylpyrroles (**4a-p**)

Azoalkene **1**[a]	ß-Ketoamide **2**[b]	Pyrrole **4**	Reaction time (hrs)	Yield[c] (%)	mp[d] (°C)
1a	**2a**	**4a**	7	75	256
	2b	**4b**	0.75	53	215-217
	2c	**4c**	5	77	270-272
	2d	**4d**	0.2	90	275-276
	2e	**4e**	2	75	286-287
	2f	**4f**	1.5	79	283-284
1b	**2a**	**4g**	1.5	63	245
	2f	**4h**	2	75	285-286
1c	**2b**	**4i**	1	60	183-184
	2f	**4j**	0.2	67	280-282
1d	**2a**	**4k**	1	70	228-229
	2f	**4l**	0.2	69	259
1e	**2b**	**4m**	0.75	65	198-199
	2f	**4n**	0.2	65	281-282
1f	**2d**	**4o**	0.2	72	224-225
1g	**2f**	**4p**	2	63	264

[a] The aroylazoalkenes **1** were prepared as previously reported.[11]
[b] The ß-ketoamides **2** were commercial materials and were used without further purification.
[c] Yield of pure isolated product.
[d] With decomposition. Melting points are uncorrected. The microanalyses were in satisfactory agreement with calculated values.

Table 2. Spectral Data of 1-Aroylamino-3-aminocarbonylpyrroles (**4a-p**)

Pyrrole	IR(nujol) ν(cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS$_{int}$) δ(ppm)
4a	3450,3340,3200,1705,1660	c,e,g,h,l,o
4b	3150,1710,1690	a,c,e,g,l,o
4c	3300,3140,1690,1645	6.8-8.3 (m, 10H)[c,e,g,n,o]
4d	3315,3190,1680,1650	c,e,g,k,n,o
4e	3315,3170,1685,1640	3.78 (s, 3H)[c,e,g,k,n,o]
4f	3310,3200,1710,1675,1650	e,g,i,n,o
4g	3370,3190,1695,1685,1670	b,c,e,h,l,o
4h	3300,3200,1700,1665	b,e,i,n,o
4i	3170,1715,1685	a,c,e,g,m,o
4j	3310,3210,1690,1655	e,g,j,n,o
4k	3430,3360,3280,1685,1660	b,c,e,h,m,o
4l	3310,3210,1700,1685,1650	b,e,j,n,o
4m	3170,1715,1685	a,c,d,e,g,m,o
4n	3230,1715,1670,1655	d,e,g,j,n,o
4o	3310,3170,1710,1665	c,e,f,g,k,n,o
4p	3290,3190,1705,1675,1660	b,e,f,i,n,o

[a] Signals at δ 0.7-1.4 ppm (m, 6H) and δ 2.9-3.6 ppm (m, 4H). These protons are magnetically not equivalent, owing to the hindered rotation about the N-CO bond.
[b] Signals at δ 1.17 ppm (t, 3H) and 4.18 ppm (q, 2H).
[c] Signal at δ 2.12 ppm (s, 3H).
[d] Signal at δ 2.35 ppm (s, 3H).
[e] Signal at δ 2.39 ppm (s, 3H).
[f] Signal at δ 3.67 ppm (s, 2H).
[g] Signal at δ 3.71 ppm (s, 3H).
[h] Signal at δ 7.12 ppm (br. s, 2H, D_2O exchange).
[i] Signal at δ 6.9-8.0 ppm (m, 15H).
[j] Signal at δ 6.9-8.0 ppm (m, 14H).
[k] Signal at δ 6.9-8.2 ppm (m, 9H).
[l] Signal at δ 7.3-8.3 ppm (m, 5H).
[m] Signal at δ 7.4-8.2 ppm (m, 4H).
[n] Signal at δ 10.28 ppm (br. s, 1H, D_2O exchange).
[o] Signal at δ 11.74 ppm (br. s, 1H, D_2O exchange).

These reactions are complete at room temperature within 0.2-7 hrs, using a molecular ratio between aroylazoalkenes and copper(II) chloride dihydrate of 20:1. The reactions occur under very mild conditions, frequently providing 1-aroylamino-3-aminocarbonylpyrroles (**4**) in good to excellent yields without complicated work-up procedures. Aroylazoalkenes (**1**) are now readily available compounds.[11] In some cases, the formation of the 1,4-adduct intermediates (**3**) are formed rapidly and their conversion to the corresponding 1-aminopyrrole derivatives (**4**) is then monitored by tlc. According to some of our previous investigations, these 1,4-adduct intermediates (**3**) are unambiguously revealed by NMR spectroscopy, exhibiting two doublets between δ 4-5 and δ 5-6 ppm assignable to the two vicinal CH protons.[4,5,7]

EXPERIMENTAL SECTION

1-Aroylamino-3-aminocarbonylpyrroles (4). General Procedure.- The aroylazoalkene (**1**) (4 mmol), the ß-ketoamide (**2**) (4 mmol), and copper(II) chloride dihydrate (0.2 mmol) were dissolved in tetrahydrofuran (4 ml). The mixture was stirred at room temperature until the reaction was complete (monitored by tlc on silica gel; elution with cyclohexane-ethyl acetate mixture 40/60 (v/v) R_f of **4c**=0.40, **4d**=0.44, **4f**=0.30, **4h**=0.50, **4j**=0.42, **4l**=0.47, **4n**=0.46, **4o**=0.33, **4p**=0.38; elution with cyclohexane-ethyl acetate mixture 10/90 (v/v) R_f of **4b**=0.56, **4e**=0.80; elution with pure ethyl acetate R_f of **4a**=0.25, **4g**=0.39, **4i**=0.66, **4k**=0.43, **4m**=0.60). In general, the precipitated product **4** is obtained by filtration in satisfactory purity. Alternatively, tetrahydrofuran was removed under reduced pressure and the residue was crystallized from methanol, providing the product **4** in satisfactory purity. Sometimes, the precipitate immediately formed was the 1,4-adduct intermediate **3**. In few cases (**4k** and **4l**), prior purification of the reaction mixture by chromatography on a silica gel (Kieselgel 60) column was necessary (elution with cyclohexane and cyclohexane/ethyl acetate mixtures). Products **4** can be further purified by recrystallization from methanol.

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