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Effect of Metal Ions in Organic Synthesis; Part XXVII. Synthesis of 3-Acyl- and 3-Alkoxycarbonyl-1-ureidopyrroles by Copper(II) Chloride-Catalyzed Reaction of Aminocarbonylazoalkenes with β-Diketones and β-Ketoesters

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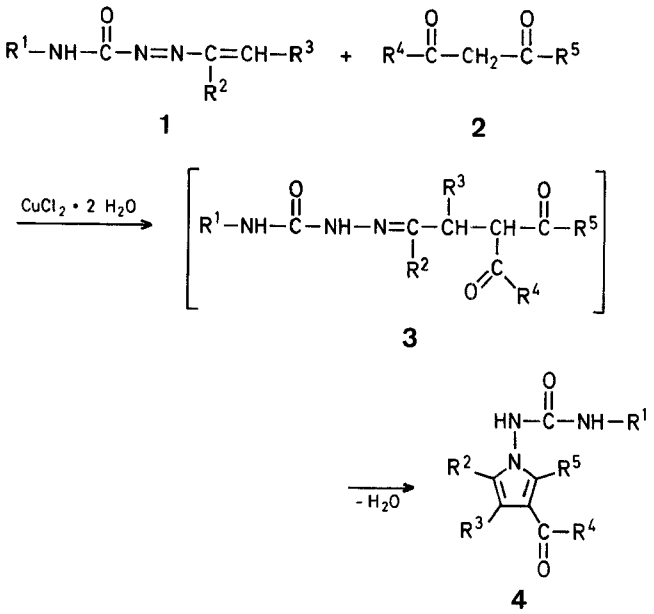
Azoalkene derivatives have been shown to be useful intermediates in organic chemistry[1-6], expecially for the synthesis of some new and interesting 1-aminopyrrole derivatives which cannot, in general, be easily prepared by other methods[7]. In fact, in the presence of catalytic amounts of copper(II) chloride dihydrate, some arylazoalkenes reacted readily with β-diketones, β-ketoesters, and β-ketoamides, affording 3-carbonyl-1-arylaminopyrroles[1,2], 3-carboxyl-1-arylaminopyrroles[1,2], and 3-aminocarbonyl-1-arylaminopyrroles[1,2,3], respectively. In analogous reaction conditions, some aminocarbonylazoalkenes, alkoxycarbonylazoalkenes, and arenesulfonylazoalkenes reacted smoothly with β-ketoamides, providing 3-aminocarbonyl-1-ureidopyrroles[4], 3-aminocarbonyl-1-alkoxycarbonylaminopyrroles[5], and 3-aminocarbonyl-1-arenesulfonylaminopyrroles[6], respectively. Considering certain structural features of the above-mentioned 1-aminopyrrole derivatives, the spectroscopic properties[8], the X-ray crystal structures[2,9], and the biological activities of some of these compounds were studied or are presently under examination.

Based on the results so far obtained, and in an attempt to further extend and generalize this synthetic procedure, we now report the one-flask synthesis of some unknown 3-acyl- and 3-alkoxycarbonyl-1-ureidopyrroles (**4**) by the copper(II) chloride-catalyzed reaction of aminocarbonylazoalkenes (**1**) with β-diketones and β-ketoesters (**2**), respectively. In the absence of the inorganic salt, under the same experimental conditions, these reagents manifest no reaction worth mentioning.

The reaction reported here occurs under mild conditions, affording 3-acyl- and 3-alkoxycarbonyl-1-ureidopyrroles (**4**) in good yields without complicated work-up procedures. Aminocarbonylazoalkenes (**1**), β-diketones and β-ketoesters (**2**), as well as copper(II) chloride dihydrate are in general relatively cheap and easily available products[4]. The reactions for the synthesis of **4aa**, **4ac**, **4ad**, **4ae**, **4bd**, **4cc**, and **4dc** are complete at room temperature within 1–24 h, using a ratio aminocarbonylazoalkenes (**1**)/copper(II) chloride dihydrate of 10/1. Under the same experimental conditions, for the synthesis of **4ab**, **4ba**, **4bb**, **4ca**, **4cb**, **4da**, and **4db**, after 24 h, the ratio aminocarbonylazoalkene (**1**)/copper(II) chloride dihydrate is increased to 5/1, and the reactions are complete after an additional 1–7 h. Especially in these latter cases,



1	R^1	R^2	R^3
a	H	CH_3	$COOCH_3$
b	H	CH_3	$COOC_2H_5$
c		CH_3	$COOCH_3$
d		CH_3	$COOC_2H_5$

2	R^4	R^5
a	CH_3	CH_3
b		CH_3
c	OCH_3	CH_3
d	OC_2H_5	CH_3
e	OCH_3	CH_2COOCH_3

frequently the formation of the 1,4-adduct intermediates (**3**) is at first detected, and then their conversion to the corresponding 1-aminopyrrole derivatives (**4**) is observed (monitored by T.L.C. on silica gel). In agreement with our previous findings[4,6], these 1,4-adduct intermediates (**3**) are unambiguously revealed by ^{1}H-N.M.R. spectroscopy, showing two doublets at $\delta \approx 4.3$ and $\delta \approx 5.6$ ppm ascribable to the two CH vicinal protons. The other mechanistic considerations on these reactions seem, in principle, to be the same as discussed in detail in previous papers[1-6].

The aminocarbonylazoalkenes **1** were prepared as previously reported[4]. The β-diketones and β-ketoesters **2**, as well as copper(II) chloride dihydrate were commerical materials and were used without further purification.

3-Acyl- and 3-Alkoxycarbonyl-1-ureidopyrroles (4); General Procedure:

The aminocarbonylazoalkene (**1a**: 2.92 mmol; **1b**: 2.70 mmol; **1c**: 2.02 mmol; **1d**: 1.91 mmol), the β-diketone or β-ketoester (**2**; 1 equiv with respect to **1**), and copper(II) chloride dihydrate (0.1 equiv with respect to **1**) are dissolved in tetrahydrofuran (5 ml). For the synthesis of **4aa**, **4ac**, **4ad**, **4ae**, **4bd**, **4cc**, and **4dc** the mixture is stirred at room temperature until the reaction is complete. For the synthesis of **4ab**, **4ba**, **4bb**, **4ca**, **4cb**, **4da**, and **4db**, after 24 h, copper(II) chloride dihydrate (0.1 equiv with respect to **1**) is futher added, and stirring is continued at room temperature until the reaction is complete. The reactions may be monitored by T.L.C. on silica gel. Tetrahydrofuran is evaporated under reduced pressure, and the residue is

Table 1. Preparation of 3-Acyl- and 3-Alkoxycarbonyl-1-ureidopyrroles (**4**)

Educts 1	2	Product 4	Ratio of 1/$CuCl_2 \cdot 2H_2O$	Reaction time [h]	Yield[a] [%]	m.p.[b] [°C]	Molecular Formula[c]
1a	**2a**	**4aa**	10/1	24	77	212–213°	$C_{11}H_{15}N_3O_4$ (253.3)
	2b	**4ab**	5/1	29	74	199–201°	$C_{16}H_{17}N_3O_4$ (315.3)
	2c	**4ac**	10/1	2	83	236–237°	$C_{11}H_{15}N_3O_5$ (269.3)
	2d	**4ad**	10/1	2.5	83	216–218°	$C_{12}H_{17}N_3O_5$ (283.3)
	2e	**4ae**	10/1	7	55	196°	$C_{13}H_{17}N_3O_7$ (327.3)
1b	**2a**	**4ba**	5/1	29	59	212–215°	$C_{12}H_{17}N_3O_4$ (267.3)
	2b	**4bb**	5/1	25	73	189–192°	$C_{17}H_{19}N_3O_4$ (329.4)
	2d	**4bd**	10/1	1	85	200–203°	$C_{13}H_{19}N_3O_5$ (297.3)
1c	**2a**	**4ca**	5/1	31	71	206–208°	$C_{17}H_{19}N_3O_4$ (329.4)
	2b	**4cb**	5/1	29	78	195°	$C_{22}H_{21}N_3O_4$ (391.4)
	2c	**4cc**	10/1	2	72	216–219°	$C_{17}H_{19}N_3O_5$ (345.4)
1d	**2a**	**4da**	5/1	30	81	193–196°	$C_{18}H_{21}N_3O_4$ (343.4)
	2b	**4db**	5/1	26	84	172–175°	$C_{23}H_{23}N_3O_4$ (405.5)
	2c	**4dc**	10/1	2.5	65	165°	$C_{18}H_{21}N_3O_5$ (359.4)

[a] Yield of pure isolated product.
[b] With decomposition. Melting points are uncorrected.
[c] The microanalyses were in satisfactory agreement with the calculated values: C ±0.35, H ±0.30, N ±0.30.

Table 2. Spectral Data of Compounds **4**

Compound	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS_{int}) δ [ppm]
4aa	3410, 3200, 1715, 1680, 1660	[b,d,e,f,h,i]
4ab	3450, 3290, 1705, 1690	3.2 (s, 3H); 7.3–7.5 (m, 5H)[b,e,h,i]
4ac	3420, 3260, 1710, 1680	3.73 (s, 6H)[c,h,i]
4ad	3410, 3260, 3200, 1710, 1675	[a,c,f,g,h,i]
4ae	3430, 3260, 3210, 1750, 1715, 1685	2.2 (s, 3H); 3.65 (s, 3H); 3.72 (s, 3H); 3.75 (s, 3H); 3.8 (s, 2H)[h,i]
4ba	3420, 3270, 3210, 1685, 1670	[a,b,d,e,g,h,i]
4bb	3410, 3260, 1710, 1675	0.7 (t, 3H); 3.67 (q, 2H); 7.3–7.8 (m, 5H)[b,e,h,i]
4bd	3420, 3260, 1705, 1680	1.23 (t, 6H); 4.17 (q, 4H)[c,h,i]
4ca	3330, 3260, 1715, 1695, 1660	6.85–7.65 (m, 5H)[b,c,e,f,i,l]
4cb	3330, 3260, 3210, 1705, 1660	3.27 (s, 3H); 6.85–7.97 (m, 10H)[b,e,i,l]
4cc	3340, 3240, 1710, 1690	3.77 (s, 6H); 6.85–7.65 (m, 5H)[c,i,l]
4da	3280, 3210, 1710, 1685, 1655	6.85–7.66 (m, 5H)[a,b,d,e,g,i,l]
4db	3330, 3260, 3210, 1705, 1660	0.73 (t, 3H); 3.7 (q, 2H); 6.83–7.93 (m, 10H)[b,e,i,l]
4dc	3290, 3200, 1700, 1650	6.86–7.7 (m, 5H)[a,c,f,g,i,l]

[a] A further signal at $\delta \approx 1.24$ ppm (t, 3H).
[b] A further signal at $\delta \approx 2.13$ ppm (s, 3H).
[c] A further signal at $\delta \approx 2.22$ ppm (s, 6H).
[d] A further signal at $\delta \approx 2.27$ ppm (s, 3H).
[e] A further signal at $\delta \approx 2.34$ ppm (s, 3H).
[f] A further signal at $\delta \approx 3.73$ ppm (s, 3H).
[g] A further signal at $\delta \approx 4.2$ ppm (q, 2H).
[h] A further signal at $\delta \approx 6.41$ ppm (br. s, 2H, D_2O exchange).
[i] A further signal at $\delta \approx 9.38$ ppm (br. s, 1H, D_2O exchange).
[l] A further signal at $\delta \approx 9.59$ ppm (br. s, 1H, D_2O exchange).

dissolved in methanol. The precipitated product **4** is isolated by suction. In general, the product is of satisfactory purity. It can be further purified by recrystallization from methanol or dichloromethane/petroleum ether (b.p. 40–60°C). In some cases, prior purification of the reaction mixture by chromatography on a silica gel column may be necessary (elution with cyclohexane and cyclohexane/ethyl acetate mixtures).

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