Effect of Metal Ions in Organic Synthesis; XVIII. A Simple and High-Yield Direct Synthesis of 1-Arylamino-3-aminocarbonylpyrroles by the Copper(II) Chloride-Catalyzed Reaction of Arylazoalkenes with 3-Oxoalkanamides

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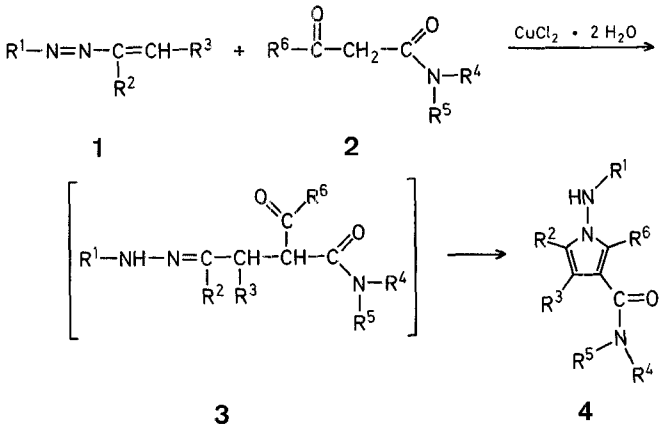
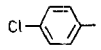
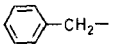
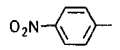
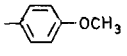
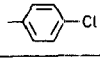
In the course of our investigations on the reactivity of metal ions in certain organic reactions[1-4], we have already reported on the stereospecific 1,4-conjugate additions of alcohols, water, and phenol to the azo-ene systems of phenylazostilbene in the presence of copper and iron ions[2]. Recently, we described the synthesis of some 1-arylaminopyrrole derivatives by the copper(II) chloride-catalyzed reaction of arylazoalkenes with β-dicarbonyl compounds and the X-ray structural analysis of



1 2 3 4

1	R^1	R^2	R^3
a			
b			
c			
d		$-(CH_2)_4-$	

2	R^4	R^5	R^6
a	H	H	CH_3
b	C_2H_5	C_2H_5	CH_3
c	H		CH_3
d	H		CH_3
e	H		CH_3

these pyrrole derivatives[3]. We now report the one-flask synthesis of some new and interesting 3-aminocarbonyl-1-arylpyrroles **(4)** by the copper(II) chloride-catalyzed reaction of arylazoalkenes **(1)** with 3-oxoalkanamides **(2)**. While no reaction takes place in the absence of copper(II) salts, the presence of catalytic amounts of copper(II) chloride dihydrate (ratio **1**/catalyst from 2/1 to 10/1) promotes the reaction satisfactorily.

The reaction conditions are mild (stirring at room temperature, a strong acid or base not being required), expensive or difficultly available reagents are not used, and the procedure is simple. Copper(II) chloride dihydrate and 3-oxoalkanamides are commercially available; the arylazoalkenes **1** are readily available[2-9] and some of them are stable. Thus, the present method which can be performed with different types of arylazoalkenes provides a convenient access to 3-aminocarbonyl-1-arylaminopyrroles **(4)**[3,10] which can in general not be easily prepared by other methods.

The ease with which the reactions proceed may be ascribed to an increased reactivity of the arylazoalkenes **(1)** and the 3-oxoalkanamides **(2)** when these reagents are present in the form of their organometallic complexes. In fact, it is known that these and analogous compounds can form complexes and chelates with several metal ions, in particular with copper(II) ion[1,3]. After the reaction, the metal ion is regenerated in its original form and can again be operative until the reaction is complete.

The reaction probably proceeds via nucleophilic attack by the activated methylene group of **2** on the C=C—N=N system of **1** to give the intermediate product **3** of a 1,4-conjugate addition (Michael type). This assumption is supported by previous investigations in which the conjugate double bond of the azo-ene system was shown to have frequently a reactivity analogous to that of other conjugate double bonds. Thus, several aliphatic and aromatic azoalkenes with or without electron-withdrawing groups on the azomoiety give [2+2]- or [4+2]-cycloadditions with some C=C dienophiles and heterodienophiles to afford heterocyclic compounds[5]. Interesting five-membered heterocycles containing P- and N-atoms (diazaphosphole derivatives) have also been obtained by cycloaddition (McCormack-type) of some phenylazoalkenes and phenyldichlorophosphine[6]. Further, some azoalkenes are known to undergo 1,4-additions with a variety of nucleophiles, producing hydrazones with simultaneous *C*-functionalization which may be useful in organic synthesis[2,3,7,8,9]. In particular, some arylazoalkenes have been shown to give 1,4-conjugate addition with compounds containing an activated methylene group[3,9]. However, the above-mentioned reactions cannot be generalized to all azoalkenes because of their different stabilities and reactivities.

The intermediate 1,4-adducts **3** are assumed to undergo an intramolecular attack by the hydrazone N^1-atom on the ketonic carbonyl group and elimination of a molecule of water to give the pyrroles **4** as shown in our previous analogous investigations[3]. In accordance with these investigations[3], also in this ring-closure process only the ketonic carbonyl group of the 3-oxoalkanamide appears to be operative. The arylazoalkenes **1** were prepared as previously reported[2-9]. The 3-oxobutanamides **2** were commercial materials and were used without purification.

3-Aminocarbonyl-1-arylaminopyrroles (4); General Procedures:

Procedure A: A solution of the 3-oxoalkanamide (**2a, c, d, e**; 10 equiv with respect to **1**) in tetrahydrofuran (3 ml) is added to a stirred solution of the arylazoalkene (**1a**: 1.76 mmol; **1b**: 1.57 mmol; **1c**: 1.68 mmol; **1d**: 2.16 mmol) in tetrahydrofuran (3 ml). Then, a solution of copper(II) chloride dihydrate (for **1a**: 0.22 mmol; **1b**: 0.196 mmol; **1c**: 0.21 mmol; **1d**: 0.216 mmol) in tetrahydrofuran (2 ml) is added and stirring is continued for 0.5–24 h (see Table 1) at room temperature until the reaction is complete (the reaction may be monitored by T.L.C. on silica gel). The mixture is extracted with ether (50 ml), washed with saturated aqueous sodium carbonate solution (5 × 20 ml) and/or 10% aqueous sodium hydroxide (5 × 20 ml), and then with water (3 × 20 ml). The organic phase is dried with anhydrous sodium sulfate, and evaporated under reduced pressure, to afford the product **4** in satisfactory purity.

Procedure B: A solution of copper(II) chloride dihydrate (for **1a**: 0.88 mmol; **1c**: 0.84 mmol; **1d**: 0.54 mmol) in tetrahydrofuran (2 ml) is added to a stirred solution of the arylazoalkene (**1a**: 1.76 mmol; **1c**: 1.68 mmol; **1d**: 2.16 mmol) in *N,N*-diethyl-3-oxobutanamide (**2b**; 15 ml). Stirring is continued at room temperature for 1.5–6.5 h (see Table 1) until the reaction is complete (as evidenced by T.L.C. on silica gel). The mixture is then worked up as described in Procedure A.

Purification of 3-Aminocarbonyl-1-arylaminopyrroles **(4)**: In general, the crude reaction products **4** are purified by crystallization from methanol, dichloromethane/petroleum ether (b.p. 40–60 °C), or hexane. In some cases, previous purification by chromatography on a silica gel column may be necessary [at first elution with cyclohexane and then with cyclohexane/ethyl acetate mixtures, gradually increasing the amount of ethyl acetate to 90/10 or 80/20 ratios].

Table 1. Preparation of 3-Aminocarbonyl-1-arylaminopyrroles **(4)**

Educts 1	2	Product 4	Ratio 1/$CuCl_2$	Procedure	Reaction time [h]	Yield[a] [%]	m.p.[b] [°C]	Molecular formula[c] or m.p. [°C] reported	
1a	**2a**	**4aa**	8/1	A	11	96	225–228°	$C_{24}H_{21}N_3O$	(367.5)
	2b	**4ab**	2/1	B	1.5	81	260°	$C_{28}H_{29}N_3O$	(423.6)
	2c	**4ac**	8/1	A	0.5	71	185–186°	$C_{30}H_{25}N_3O$	(443.6)
	2d	**4ad**	8/1	A	1	75	144–145°	$C_{31}H_{27}N_3O_2$	(473.6)
	2e	**4ae**	8/1	A	0.5	75	188–189°	$C_{30}H_{24}ClN_3O$	(478.0)
1b	**2a**	**4ba**	8/1	A	24	80	228°	$C_{24}H_{20}ClN_3O$	(401.9)
	2c	**4bc**	8/1	A	8	81	234°	$C_{30}H_{24}ClN_3O$	(478.0)
	2d	**4bd**	8/1	A	8	76	225°	$C_{31}H_{26}ClN_3O_2$	(508.0)
	2e	**4be**	8/1	A	3	71	238°	$C_{30}H_{23}Cl_2N_3O$	(512.5)
1c	**2a**	**4ca**	8/1	A	8	78	221–222°	$C_{25}H_{23}N_3O$	(381.5)
	2b	**4cb**	2/1	B	5	50	202–204°	$C_{29}H_{31}N_3O$	(437.6)
	2c	**4cc**	8/1	A	1	35	157°	$C_{31}H_{27}N_3O$	(457.6)
	2d	**4cd**	8/1	A	3.5	40	174–175°	$C_{32}H_{29}N_3O_2$	(487.6)
1d	**2b**	**4db**	4/1	B	6.5	80	225°	$C_{20}H_{26}N_4O_3$	(370.5)
	2c	**4dc**	10/1	A	1	80	162–164°	$C_{22}H_{22}N_4O_3$	(390.5)
	2d	**4dd**	10/1	A	2	75	226–228°	$C_{23}H_{24}N_4O_4$	(420.5)
	2e	**4de**	10/1	A	1	72	243°	$C_{22}H_{21}ClN_4O_3$	(424.9)

[a] Yield of pure isolated product.
[b] 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. ($CDCl_3$/TMS_{int})[a] δ [ppm]
4aa	3485, 3255, 3140, 1645	6.3–7.4 (m, 16H; at 6.70, s, D_2O exchange)[b,c]
4ab	3210, 1600	0.5–1.4 (m, 6H); 2.1 (s, 3H); 2.5–4.0 (m, 4H); 6.4–7.6 (m, 16H; at 6.87, s, D_2O exchange)[d]
4ac	3400, 3210, 1640	6.3–7.55 (m, 22H; at 6.7, s, D_2O exchange)[b]
4ad	3400, 3240, 1640	3.75 (s, 3H); 6.3–7.4 (m, 21H; at 6.73, s, D_2O exchange)[b]
4ae	3390, 3295, 1640	6.3–7.7 (m, 21H; at 6.76, s, D_2O exchange)[b]
4ba	3490, 3245, 3160, 1645	6.3–7.3 (m, 15H; at 6.77, s, D_2O exchange)[b,c]
4bc	3395, 3345, 1650	6.3–7.8 (m, 21H; at 6.83 and 6.84, 2s, D_2O exchange)[b]
4bd	3425, 3250, 1655	3.73 (s, 3H); 6.3–7.5 (m, 20H; at 6.67, s, D_2O exchange)[b]
4be	3425, 3265, 1655	6.3–7.8 (m, 20H; at 6.73 and 6.98, 2s, D_2O exchange)[b]
4ca	3485, 3240, 3160, 1655	3.6 (s, 2H); 5.95–7.6 (m, 16H; at 6.0, s, D_2O exchange)[b,c]
4cb	3200, 1600	0.5–1.3 (m, 6H); 2.13 (s, 3H); 2.5–3.7 (m, 4H); 3.87 (s, 2H); 6.1–7.6 (m, 16H; at 6.16, s, D_2O exchange)[d]
4cc	3420, 3220, 1650	3.67 (s, 2H); 6.0–7.7 (m, 22H; at 6.05, s, D_2O exchange)[b]
4cd	3420, 3225, 1635	3.73 (s, 5H); 6.1–7.65 (m, 21H; at 6.15, s, D_2O exchange)[b]
4db	3190, 1600	0.6–2.8 (m, 17H; at 1.65, s); 2.9–4.0 (m, 4H); 6.5 (d, 2H, J=9 Hz); 8.1 (d, 2H, J=9 Hz); 10.2 (s, 1H, D_2O exchange)[d]
4dc	3360, 3220, 1640	1.45–2.9 (m, 11H; at 2.3, s); 6.35–8.4 (m, 9H; at 6.57 and 8.24, 2d, J=9 Hz); 9.3 and 10.1 (2s, 2H, D_2O exchange)[e]
4dd	3340, 3200, 1635	1.4–3.0 (m, 11H; at 2.25, s); 3.78 (s, 3H); 6.52 (d, 2H, J=9 Hz); 6.88 (d, 2H, J=9.1 Hz); 7.65 (d, 2H, J=9.1 Hz); 8.18 (d, 2H, J=9 Hz); 9.1 and 10.1 (2s, 2H, D_2O exchange)[e]
4de	3455, 3265, 1650	1.3–3.0 (m, 11H; at 2.27, s); 6.55 (d, 2H, J=9 Hz); 7.35 (d, 2H, J=9.2 Hz); 7.78 (d, 2H, J=9.2 Hz); 8.18 (d, 2H, J=9 Hz); 9.43 and 10.1 (2s, 2H, D_2O exchange)[e]

[a] A detailed conformational study of these derivatives by ^{1}H- and ^{13}C-N.M.R. spectrometry is in progress.

[b] These products gave a signal at $\delta \approx 2.55$ ppm (s, 3H).

[c] These products gave a broad signal at $\delta \sim 5.26$ ppm (2H), showing D_2O exchange.

[d] The protons of the $N(C_2H_5)_2$ group are magnetically not equivalent, owing to the hindered rotation about the N—CO bond.

[e] In DMSO-d_6/TMS_{int}.

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