Effect of Metal Ions in Organic Synthesis. Part XXXI. Synthesis of New 3-Carbonyl- and 3-Carboxy-1-heterocyclaminopyrroles by Copper(II) Chloride-Catalyzed Reaction of Heterocyclic Azoalkenes

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The direct synthesis of a new class of unknown 1-heterocyclamino-3-carbonylpyrroles and 1-heterocyclamino-3-carboxypyrroles by copper(II) chloride-catalyzed reaction of heterocyclic conjugated azoalkene derivatives with β-diketones and β-ketoesters is reported.

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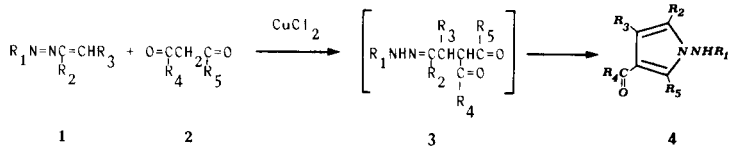
Recently, we increased the investigations in order to further extend the applications of the direct method for the preparation of new classes of unknown 1-aminopyrrole derivatives widely substituted both at the carbon and nitrogen atoms of the pyrrole ring. Thus, 1-arylamino-3-carbonylpyrroles [1,2a,b], 1-arylamino-3-carboxypyrroles [1, 2a,b], 1-arylamino-3-aminocarbonylpyrroles, [1,2c], 1-ureido-3-carbonylpyrroles [2d], 1-ureido-3-carboxypyrroles [2d], 1-ureido-3-aminocarbonylpyrroles [2e], 1-alkoxycarbonylamino-3-carbonylpyrroles [2f], 1-alkoxycarbonylamino-3-carboxypyrroles [2f], 1-alkoxycarbonylamino-3-aminocarbonylpyrroles [2g], 1-arylsulfonylamino-3-carboxypyrroles [2h], 1-arylsulfonylamino-3-aminocarbonylpyrroles [2i], and 1-aroylamino-3-aminocarbonylpyrroles [2j] were previously reported. In some cases, nmr spectra [3], crystal structures [2a,4], pharmacological and phitopharmacological activities (*i.e.* anticancer [5], viricide, insecticide, bactericide, fungicide, nematicide, herbicide *etc* [6]) were studied or are presently under examination. Moreover, it appears unlikely that these compounds may be easily prepared by other methods [7].

The procedure mentioned above is generally based on the copper(II) ions-catalyzed reaction between different azoalkenes and β-diketones, β-ketoesters or β-ketoamides. Considering these syntheses to be largely dependent from the nature of the conjugated azoalkenes, the preparation of new classes of these latter derivatives containing different functional groups was also studied in detail [8]. In particular, we recently reported the synthesis of new heterocyclic conjugated azoalkenes [8b].

Some of these compounds **1a-e** demonstrated to represent useful intermediates for the synthesis of interesting 1-heterocyclamino-3-carbonylpyrroles and 1-heterocyclamino-3-carboxypyrroles **4a-l** by their reaction with β-diketones and β-ketoesters **2a-h** under copper(II) chloride catalysis.

These reactions readily occur with commercial purity materials and under mild conditions, frequently providing

Scheme



1 2 3 4

1	R_1	R_2	R_3
a	3-Nitro-2-pyridyl	CH_3	$COOCH_3$
b	3-Nitro-2-pyridyl	p-$NO_2C_6H_4$	$COOC_2H_5$
c	2-Pyrimidyl	CH_3	$COOCH_3$
d	2-Pyrimidyl	CH_3	$COOCH_2C_6H_5$
e	2-Benzothiazol	CH_3	$COOCH_3$

2	R_4	R_5
a	CH_3	CH_3
b	C_6H_5	CH_3
c	C_6H_5	C_6H_5
d	OCH_3	CH_3
e	OC_2H_5	CH_3
f	OC_2H_5	C_6H_5
g	OC_2H_5	p-$NO_2C_6H_4$
h	$OCH_2C_6H_5$	CH_3

Table

Molecular Ratios Between Heterocyclic Azoalkenes and β-Diketones or β-Ketoesters (**1:2**), Between Heterocyclic Azoalkenes and Copper(II) Chloride (**1:*M***), Reaction Procedure, Times, Yields, and Melting Points of the Reaction Products

Azoalkene No.	β-Dicarbonyle No.	Pyrrole No.	1:2	1:*M*	Procedure [a]	Time (hours)	Yields (%)	Mp (°C) [b]
1a	**2a**	**4a**	1:10	10:1	A	11	67	215-216
	2b	**4b**	1:10	15:1	A	96	94	210
	2c	**4c**	1:10	2:1	A	120	62	210-211
	2d	**4d**	1:1	5:1	B	3	60	258-260
	2e	**4e**	1:10	20:1	A	144	85	167-168
	2f	**4f**	1:10	2:1	A	120	75	198-200
1b	**2d**	**4g**	1:1	10:1	A	12	79	165-166
	2g	**4h**	1:1	10:1	A	11	73	254-255
1c	**2d**	**4i**	1:10	5:1	B	3	43	220-222
1d	**2d**	**4j**	1:10	20:1	A	16	90	159
	2h	**4k**	1:10	20:1	B	168	64	130
1e	**2d**	**4l**	1:10	5:1	A	72	82	187-190

[a] See experimental. [b] Melting points are uncorrected.

1-heterocyclamino-3-carbonylpyrroles and 1-heterocyclamino-3-carboxypyrroles **4** in good yields without complicated procedures for their isolation.

With the exception of three cases (**4d, 4i** and **4k**), the remaining reactions clearly exhibits the 1,4-adduct intermediate **3** formation for which the presence of copper(II) chloride seems not to be necessary (monitored by silica gel tlc), while the presence of this inorganic salt is absolutely necessary for the subsequent pyrrole ring closure. According to our previous findings [2], this behaviour is unambiguously detected by ^{1}H nmr (two doublet between $\delta = 4 \div 5$ and $\delta = 5 \div 6$ ppm, respectively imputable to the two CH vicinal protons of the adduct).

EXPERIMENTAL

The β-diketones and β-ketoesters **2**, as well as anhydrous copper(II) chloride were commercial materials, and were used without further purification. Ir and ^{1}H nmr were recorded on a Perkin-Elmer 298 and a Varian EM-360L spectrometer at 60 MHz, respectively. Kieselgel 60 was used for chromatography.

Heterocyclic Azoalkenes **1a-e**.

These compounds were prepared as previously reported in detail [8b].

Procedure A for the Synthesis of Compounds **4a-c, 4e-h, 4i** and **4l**.

To a stirred solution of heterocyclic azoalkenes **1a-b** and **1d-e** (2 mmoles) dissolved in tetrahydrofuran (2 ml) was added β-diketones or β-ketoesters **2a-h** (see Table) dissolved in tetahydrofuran (6 ml). The mixture was stirred at room temperature, until azoalkenes completely reacted, producing the respective 1,4-adduct intermediate **3** (monitored by silica gel tlc). For the synthesis of **4a** the mixture was heated under reflux. Then anhydrous copper(II) chloride (see Table) was added and the mixture was stirred at room temperature, until the reaction was complete, affording the relative product **4** (monitored by silica gel tlc).

Tetrahydrofuran was evaporated under reduced pressure, and the reaction mixture was poured into ether, washed several times with 1% aqueous sulfuric acid solution, then with 10% aqueous sodium carbonate solution, and finally with water. The organic phase was separated, dried with anhydrous sodium sulfate, and evaporated under reduced pressure, providing the crude product in satisfactory purity. This product may be further purified by chromatography on a silica gel column (at first elution with cyclohexane and then with cyclohexane/ethyl acetate mixtures, gradually increasing the amount of ethyl acetate to a 80/20 (v/v) ratio). The product **4** was crystallized with methanol.

Procedure B for the Synthesis of Compounds **4d, 4i** and **4k**.

The heterocyclic azoalkenes **1a, 1c** and **1d** (2 mmoles), the β-ketoesters **2d** and **2h** (see Table), and anhydrous copper(II) chloride (see Table) were dissolved in tetrahydrofuran (8 ml). The mixture was stirred at room temperature until the reaction was complete, affording the relative product **4** (monitored by silica gel tlc). Tetrahydrofuran was evaporated under reduced pressure and the product was isolated in satisfactory purity by chromatography on a silica gel column, as described above in detail. The product was further purified by crystallization with methanol.

2,5-Dimethyl-3-carbomethoxy-4-acetyl-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4a**).

This compound was obtained in a yield of 67%, mp 215-216° (uncorrected); ir (nujol): 3340 (NH), 1720 (COO), 1690 (C=O), 1610 (pyridyl), 1530 and 1350 cm^{-1} (NO_2); ^{1}H nmr (dimethylsulfoxide-d_6, TMS): δ 2.1 (3H, s, Me), 2.24 (3H, s, Me), 2.3 (3H, s, Me), 3.75 (3H, s, COOMe), 6.97-7.3 (1H, m, pyridyl), 8.37-8.77 (2H, m, pyridyl), 11.03 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{15}H_{16}N_4O_5$: C, 54.22; H, 4.85; N, 16.86. Found: C, 54.48; H, 4.78; N, 16.79.

2,5-Dimethyl-3-carbomethoxy-4-benzoyl-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4b**).

This compound was obtained in a yield of 94%, mp 210° (uncorrected); ir (nujol): 3340 (NH), 1720 (COO), 1640 (C=O), 1610 (pyridyl and phenyl), 1530 and 1350 cm^{-1} (NO_2); ^{1}H nmr (dimethylsulfoxide-d_6, TMS): δ 2.05 (3H, s, Me), 2.3 (3H, s, Me), 3.23 (3H, s, COOMe), 7.0-7.33 (1H, m, pyridyl), 8.43-8.8 (2H, m, pyridyl), 7.33-7.9 (5H, m, phenyl), 11.1 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 61.19; H, 4.33; N, 14.07.

2-Methyl-3-carbomethoxy-4-benzoyl-5-phenyl-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4c**).

This compound was obtained in a yield of 62%, mp 210-211° (uncorrected); ir (nujol): 3290 (NH), 1700 (COO), 1650 (C=O), 1600 (pyridyl and phenyl), 1530 and 1340 cm^{-1} (NO_2); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 2.38 (3H, s, Me), 3.4 (3H, s, COOMe), 6.83-7.93 and 8.3-8.63 (13H, m, pyridyl and phenyl), 11.17 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{25}H_{20}N_4O_5$: C, 65.78; H, 4.42; N, 12.27. Found: C, 65.51; H, 4.54; N, 12.33.

2,5-Dimethyl-3,4-dicarbomethoxy-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4d**).

This compound was obtained in a yield of 60%, mp 258-260° (uncorrected); ir (nujol): 3325 (NH), 1700 (COO), 1610 (pyridyl), 1530 and 1350 cm^{-1} (NO_2); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 2.13 (6H, s, 2Me), 3.74 (6H, s, 2COOMe), 6.95-7.3 (1H, m, pyridyl), 8.33-8.73 (2H, m, pyridyl), 11.03 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{15}H_{16}N_4O_6$: C, 51.72; H, 4.63; N, 16.08. Found: C, 52.00; H, 4.44; N, 15.99.

2,5-Dimethyl-3-carbomethoxy-4-carbethoxy-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4e**).

This compound was obtained in a yield of 85%, mp 167-168° (uncorrected); ir (nujol): 3370 (NH), 1700 (COO), 1610 (pyridyl), 1535 and 1345 cm^{-1} (NO_2); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 1.23 (3H, t, COOEt), 2.15 (6H, s, 2Me), 3.73 (3H, s, COOMe), 4.17 (2H, q, COOEt), 6.93-7.29 (1H, m, pyridyl), 8.35-8.78 (2H, m, pyridyl), 11.03 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 5.01; N, 15.46. Found: C, 53.34; H, 4.91; N, 15.28.

2-Methyl-3-carbomethoxy-4-carbethoxy-5-phenyl-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4f**).

This compound was obtained in a yield of 75%, mp 198-200° (uncorrected); ir (nujol): 3330 (NH), 1700 (COO), 1610 (pyridyl and phenyl), 1535 and 1345 cm^{-1} (NO_2); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 1.13 (3H, t, COOEt), 2.28 (3H, s, Me), 3.77 (3H, s, COOMe), 4.1 (2H, q, COOEt), 6.8-7.63 and 8.17-8.67 (8H, m, pyridyl and phenyl), 11.13 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{21}H_{20}N_4O_6$: C, 59.43; H, 4.75; N, 13.20. Found: C, 59.27; H, 4.87; N, 13.32.

2-(*p*-Nitrophenyl)-3-carbethoxy-4-carbomethoxy-5-methyl-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4g**).

This compound was obtained in a yield of 79%, mp 165-166° (uncorrected); ir (nujol): 3320 (NH), 1690 (COO), 1600 (pyridyl and phenyl), 1525 and 1340 cm^{-1} (NO_2); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 1.15 (3H, t, COOEt), 2.3 (3H, s, Me), 3.8 (3H, s, COOMe), 4.15 (2H, q, COOEt), 6.9-7.27 (1H, m, pyridyl), 8.37-8.77 (2H, m, pyridyl), 7.97 (4H, q, J = 9 Hz, phenyl), 1.33 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{21}H_{19}N_5O_8$: C, 53.73; H, 4.08; N, 14.92. Found: C, 53.53; H, 4.18; N, 15.07.

2,5-(*p,p'*-Dinitrophenyl)-3,4-dicarbethoxy-*N*-(3'-nitro-2'-pyridyl)-1-aminopyrrole (**4h**).

This compound was obtained in a yield of 73%, mp 254-255° (uncorrected); ir (nujol): 3330 (NH), 1700 (COO), 1610 (pyridyl and phenyl), 1535 and 1340 cm^{-1} (NO_2); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 1.17 (3H, t, COOEt), 4.13 (2H, q, COOEt), 6.78-7.1 (1H, m, pyridyl), 7.6-8.5 (10H, m, pyridyl and phenyl), 11.43 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{27}H_{22}N_6O_{10}$: C, 54.92; H, 3.76; N, 14.23. Found: C, 55.09; H, 3.69; N, 14.03.

2,5-Dimethyl-3,4-dicarbomethoxy-*N*-(2'-pyrimidyl)-1-aminopyrrole (**4i**).

This compound was obtained in a yield of 43%, mp 220-222° (uncorrected); ir (nujol): 3320 (NH), 1710 (COO), 1580 cm^{-1} (pyrimidyl); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 2.13 (6H, s, 2Me), 3.74 (6H, s, COOMe), 6.98 (1H, t, pyrimidyl), 8.51 (2H, d, pyrimidyl), 10.5 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.06; H, 5.46; N, 18.61.

2,5-Dimethyl-3-carbobenzyloxy-4-carbomethoxy-*N*-(2'-pyrimidyl)-1-aminopyrrole (**4j**).

This compound was obtained in a yield of 90%, mp 159° (uncorrected); ir (nujol): 3230 (NH), 1690 (COO), 1600 (phenyl), 1580 cm^{-1} (pyrimidyl); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 2.15 (3H, s, Me), 2.2 (3H, s, Me), 3.7 (3H, s, COOMe), 5.23 (2H, s, CH_2), 6.95 (1H, t, pyrimidyl), 7.45 (5H, s, phenyl), 8.5 (2H, d, pyrimidyl), 10.52 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.43; H, 5.17; N, 14.53.

2,5-Dimethyl-3,4-dicarbobenzyloxy-*N*-(2'-pyrimidyl)-1-aminopyrrole (**4k**).

This compound was obtained in a yield of 64%, mp 130° (uncorrected); ir (nujol): 3220 (NH), 1710 (COO), 1600 (phenyl), 1580 cm^{-1} (pyrimidyl); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 2.17 (6H, s, 2Me), 5.17 (4H, s, $2CH_2$), 6.97 (1H, t, pyrimidyl), 7.42 (10H, s, phenyl), 8.48 (2H, d, pyrimidyl), 10.52 ppm (1H, s broad, NH, deuterium oxide exchange).

Anal. Calcd. for $C_{26}H_{24}N_4O_4$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.69; H, 5.18; N, 13.89.

2,5-Dimethyl-3,4-dicarbomethoxy-*N*-(2'-benzothiazol)-1-aminopyrrole (**4l**).

This compound was obtained in a yield of 82%, mp 187-190° (uncorrected); ir (nujol): 3330 (NH), 1700 (COO), 1600 cm^{-1} (phenyl); ^1H nmr (dimethylsulfoxide-d_6, TMS): δ 2.3 (6H, s, 2Me), 3.79 (6H, s, 2COOMe), 6.93-7.97 ppm (5H, m, phenyl and NH; 1H, deuterium oxide exchange).

Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.62; H, 4.69; N, 11.77.

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