

Effect of Metal Ions in Organic Synthesis. Part XIV.
A Mild, Simple, and Convenient Method for the Synthesis of
1-(Arylamino)pyrrole Derivatives by Copper(II) Ion-Catalyzed Reaction of
(Arylazo)alkenes and 1,3-Dicarbonyl Compounds

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A mild, simple and convenient method for the synthesis of some 1-(arylamino)pyrrole derivatives by copper(II) ion-catalyzed reaction of (arylazo)alkenes and 1,3-dicarbonyl compounds is reported. These reactions take place under magnetic stirring at room temperature, do not require a strong acid or base, nor expensive or difficultly available reagents, nor even complicated procedures. The synthesis seems to be successfully applicable to different (arylazo)alkenes, 1,3-diketones and β -ketoesters, and frequently occurs with good yields.

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Within the last few years the role and effect of some metal ions in certain organic reactions have been studied in our laboratories [1]. In particular, we already reported the stereospecific 1,4-conjugate additions of alcohols, water and phenol to the azo-ene system of (phenylazo)stilbene in the presence of copper and iron ions [2]. More recently, we reported the synthesis and X-ray crystal structure of some 1-(arylamino)pyrrole derivatives by the reaction of (arylazo)alkenes and 1,3-dicarbonyl compounds in the presence of copper(II) chloride dihydrate [3].

Continuing these investigations, we extended these latter reactions to different 1,3-dicarbonyl compounds. In this paper, the synthesis of some new and interesting 1-(arylamino)pyrrole derivatives is described. Furthermore, the

yields of some 1-(arylamino)pyrroles reported in the previous paper were substantially improved. In some cases, the molecular ratio between the (arylazo)alkenes and copper(II) chloride dihydrate was increased compared to those already reported, as proof of the catalytic role for the copper(II) ions previously hypothesized. Finally, in all cases also the conditions and procedures of the reactions were further simplified [3].

Results and Discussion.

While in the absence of copper(II) chloride dihydrate (**M**) no reaction was observed, in the presence of this inorganic salt, (arylazo)alkenes **1a-c** and 1,3-dicarbonyl compounds **2a-f** easily react, producing the 1-(arylamino)pyrrole derivatives **4a-p**, as shown in the following Scheme.

Table

Molecular Ratios Between (Arylazo)alkenes and Copper(II) Chloride Dihydrate (1:M),
Reaction Procedures and Times, Yields, and Melting Points of the Reaction Products

Azoalkene No.	1,3-dicarbonyl No.	pyrrole No.	1:M	procedure (a)	time (hours)	yields (%)	mp (°C) (b)
1a	2a	4a	8:1	A	1	85	145-146
	2b	4b	8:1	B	1	75	134-135
	2c	4c	8:1	B	1	75	161-162
	2d	4d	8:1	C	24	65	173-174
	2e	4e	8:1	C	1	50	144-145
	2f	4f	8:1	C	8	55	212-213
1b	2a	4g	8:1	A	1	75	161-162
	2b	4h	8:1	B	1	40	148-149
	2c	4i	8:1	B	1	40	108-109
	2d	4l	8:1	C	22	55	177-178
1c	2b	4m	10:1	B	1	50	174-175
	2c	4n	10:1	B	1	75	153-154
	2d	4o	10:1	C	3	55	204-205
	2e	4p	10:1	C	1	50	215-217

(a) See Experimental. (b) Melting points are uncorrected.

At present, further investigations are in progress in our laboratories to extend and generalize these and related reactions, and elucidate the kinetic and mechanistic aspects.

EXPERIMENTAL

(Arylazo)alkenes **1a-c**.

These compounds were synthesized as previously reported [2,3,4-7].

1,3-Dicarbonyl Derivatives **2a-f**.

These compounds were commercial materials and were used without further purification.

Procedure A for the Synthesis of Compounds **4a** and **4g**.

Copper(II) chloride dihydrate (0.22 and 0.21 mmole, respectively) dissolved in 2,4-pentanedione **2a** (7 ml) was added to a solution of (arylazo)alkene (1.76 mmoles of (phenylazo)stilbene **1a** or 1.68 mmoles of (phenylazo)diphenylpropene **1b**, respectively) in 2,4-pentanedione (7 ml). The mixture was stirred magnetically at room temperature during 1 hour, until the reaction was completed (monitored by silica gel tlc). The reaction mixture was poured into ether, washed several times with saturated aqueous sodium carbonate solution and then with water. The organic layer was dried with anhydrous sodium sulfate, and after evaporation under reduced pressure, it provided the relative 1-(phenylamino)pyrrole derivatives **4a** and **4g**.

Procedure B for the Synthesis of Compounds **4b-c**, **4h-i** and **4m-n**.

Copper(II) chloride dihydrate (0.22, 0.21 and 0.216 mmole, respectively) dissolved in tetrahydrofuran (3 ml) was added to a solution of (arylazo)alkene (1.76 mmoles of (phenylazo)stilbene **1a**, 1.68 mmoles of (phenylazo)diphenylpropene **1b** or 2.16 mmoles of [*p*-nitrophenyl]azocyclohexene **1c**, respectively) in methyl or ethyl acetate **2b** and **2c** (15 ml). The mixture was stirred magnetically at room temperature during 1 hour, until the reaction was completed (monitored by silica gel tlc). Afterward the reaction was treated as described above in detail, providing the relative 1-(arylamino)pyrrole derivatives **4b-c**, **4h-i** and **4m-n**.

Procedure C for the Synthesis of Compounds **4d-f**, **4l** and **4o-p**.

1-Phenyl-1,3-butanedione **2d**, 1,3-diphenyl-1,3-propanedione **2e** or 1,3-cyclohexanedione **2f**, ten times more than the stoichiometric amount, dissolved in tetrahydrofuran (3 ml) was added to a solution of (arylazo)alkene (1.76 mmoles of (phenylazo)stilbene **1a**, 1.68 mmoles of (phenylazo)diphenylpropene **1b** or 2.16 mmoles of [*p*-nitrophenyl]azocyclohexene **1c**, respectively) in tetrahydrofuran (3 ml) and then copper(II) chloride dihydrate (0.22, 0.21 and 0.216 mmole, respectively) dissolved in tetrahydrofuran (2 ml) was added. The mixture was stirred magnetically at room temperature during 1-24 hours (see Table), until the reaction was completed (monitored by silica gel tlc). Afterward the reaction was treated as described above in detail, providing the relative 1-(arylamino)pyrrole derivatives **4d-f**, **4l** and **4o-p**. In this case the ethereal layer may be conveniently washed with 5% aqueous sodium hydroxide.

Purification of Compounds **4a-p**.

In general the crude reaction products **4a-p** were purified by crystallization with methylene chloride-petroleum ether (40-60°) or *n*-hexane. In the particular case of the products **4b**, **4e-f**, **4h-i**, **4m-n** and **4p** a preliminary 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 a 90/10 (v/v) ratio).

Analytical Data of Compounds **4a-p**.

The analytical data of 1-phenylamino-2,3-diphenyl-4-acetyl-5-methylpyrrole **4a**, 1-phenylamino-2,3-diphenyl-4-carbomethoxy-5-methylpyrrole **4c**, 1-phenylamino-2,3-diphenyl-4-oxo-4,5,6,7-tetrahydroindole **4f**, 1-phenyl-

amino-2-benzyl-3-phenyl-4-acetyl-5-methylpyrrole **4g** and 1-(*p*-nitrophenylamino)-2-methyl-3-carbomethoxy-4,5,6,7-tetrahydroindole **4n** were reported in detail in our previous paper [3,10].

1-Phenylamino-2,3-diphenyl-4-carbomethoxy-5-methylpyrrole **4b**.

This compound was obtained in a yield of 75%, mp 134-135° (uncorrected); ir (nujol): 3300 (NH), 1675 (COO), 1605 cm⁻¹ (aromatic); ¹H nmr (deuteriochloroform, TMS): δ 2.50 (3H, s), 3.60 (3H, s), 6.25-7.35 (16H, m; at 6.60, 1H, s, deuterium oxide exchange).

Anal. Calcd. for C₂₅H₂₂N₂O₂: C, 78.5; H, 5.8; N, 7.3. Found: C, 78.7; H, 5.9; N, 7.1.

1-Phenylamino-2,3-diphenyl-4-benzoyl-5-methylpyrrole **4d**.

This compound was obtained in a yield of 65%, mp 173-174° (uncorrected); ir (nujol): 3240 (NH), 1625 (C=O), 1600 cm⁻¹ (aromatic); ¹H nmr (deuteriochloroform, TMS): δ 2.35 (3H, s), 6.35-7.90 (21H, m; at 6.85, 1H, s, deuterium oxide exchange).

Anal. Calcd. for C₃₀H₂₄N₂O: C, 84.1; H, 5.7; N, 6.5. Found: C, 83.9; H, 5.6; N, 6.6.

1-Phenylamino-2,3,5-triphenyl-4-benzoylpyrrole **4e**.

This compound was obtained in a yield of 50%, mp 144-145° (uncorrected); ir (nujol): 3320 (NH), 1690 (C=O), 1600 cm⁻¹ (aromatic); ¹H nmr (deuteriochloroform, TMS): δ 6.30-8.15 (m).

Anal. Calcd. for C₃₅H₂₄N₂O: C, 85.7; H, 5.3; N, 5.7. Found: C, 85.9; H, 5.2; N, 5.6.

1-Phenylamino-2-benzyl-3-phenyl-4-carbomethoxy-5-methylpyrrole **4h**.

This compound was obtained in a yield of 40%, mp 148-149° (uncorrected); ir (nujol): 3250 (NH), 1670 (COO), 1600 cm⁻¹ (aromatic); ¹H nmr (deuteriochloroform, TMS): δ 2.45 (3H, s), 3.60 (5H, s), 5.90 (1H, s, deuterium oxide exchange), 6.25-7.45 (15H, m).

Anal. Calcd. for C₂₆H₂₄N₂O₂: C, 78.8; H, 6.1; N, 7.1. Found: C, 78.5; H, 6.3; N, 7.3.

1-Phenylamino-2-benzyl-3-phenyl-4-carbomethoxy-5-methylpyrrole **4i**.

This compound was obtained in a yield of 40%, mp 108-109° (uncorrected); ir (nujol): 3305 (NH), 1665 (COO), 1605 cm⁻¹ (aromatic); ¹H nmr (deuteriochloroform, TMS): δ 1.05 (3H, t, J = 7 Hz), 2.50 (3H, s), 3.65 (2H, s), 4.10 (2H, q, J = 7 Hz), 5.95 (1H, s, deuterium oxide exchange), 6.30-7.50 (15H, m).

Anal. Calcd. for C₂₇H₂₆N₂O₂: C, 79.0; H, 6.4; N, 6.8. Found: C, 79.3; H, 6.2; N, 6.7.

1-Phenylamino-2-benzyl-3-phenyl-4-benzoyl-5-methylpyrrole **4l**.

This compound was obtained in a yield of 55%, mp 177-178° (uncorrected); ir (nujol): 3250 (NH), 1620 (C=O), 1600 cm⁻¹ (aromatic); ¹H nmr (deuteriochloroform, TMS): δ 2.30 (3H, s), 3.80 (2H, s), 6.00 (1H, s, deuterium oxide exchange), 6.10-7.85 (20H, m).

Anal. Calcd. for C₃₁H₂₆N₂O: C, 84.1; H, 5.9; N, 6.3. Found: C, 84.3; H, 6.0; N, 6.4.

1-(*p*-Nitrophenylamino)-2-methyl-3-carbomethoxy-4,5,6,7-tetrahydroindole **4m**.

This compound was obtained in a yield of 50%, mp 174-175° (uncorrected); ir (nujol): 3270 (NH), 1660 (COO), 1600 (aromatic), 1500 and 1330 cm⁻¹ (NO₂); ¹H nmr (deuteriochloroform, TMS): δ 1.60-3.00 (11H, m, s at 2.40), 3.80 (3H, s), 6.50 (2H, d, J = 9 Hz), 7.30 (1H, s, deuterium oxide exchange), 8.20 (2H, d, J = 9 Hz).

Anal. Calcd. for C₁₇H₁₉N₃O₄: C, 62.0; H, 5.8; N, 12.8. Found: C, 61.8; H, 5.7; N, 12.6.

1-(*p*-Nitrophenylamino)-2-methyl-3-phenyl-4,5,6,7-tetrahydroindole **4o**.

This compound was obtained in a yield of 55%, mp 204-205° (uncorrected); ir (nujol): 3210 (NH), 1615 (C=O), 1595 (aromatic), 1500 and 1330 cm⁻¹ (NO₂); ¹H nmr (deuteriochloroform, TMS): δ 1.50-2.55 (11H, m; s at 2.00), 6.55 (2H, d, J = 9 Hz), 7.25-8.10 (6H, m; at 8.00, 1H, s, deuterium oxide exchange), 8.20 (2H, d, J = 9 Hz).

Anal. Calcd. for C₂₁H₂₁N₃O₂: C, 72.6; H, 6.1; N, 12.1. Found: C, 72.2; H,

6.2; N, 12.3.

1-(p-Nitrophenylamino)-2,3-diphenyl-4,5,6,7-tetrahydroindole **4p**. This compound was obtained in a yield of 50%, mp 215-217° (uncorrected); ir (nujol): 3315 (NH), 1690 (C=O), 1595 (aromatic), 1500 and 1320 cm⁻¹ (NO₂); ¹H nmr (deuteriochloroform, TMS): δ 1.50-2.85 (8H, m), 6.50 (2H, d, J = 9 Hz), 7.00-7.70 (11H, m, at 7.40, 1H, s, deuterium oxide exchange), 8.10 (2H, d, J = 9 Hz).

Anal. Calcd. for C₂₆H₂₃N₃O₂: C, 76.3; H, 5.7; N, 10.3. Found: C, 76.1; H, 5.6; N, 10.2.

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REFERENCES AND NOTES

- [1] O. Attanasi and S. Gasperoni, *Gazz. Chim. Ital.*, **108**, 137 (1978); O. Attanasi, S. Gasperoni and C. Carletti, *Chim. Ind. (Milano)*, **60**, 654 (1978); O. Attanasi, S. Gasperoni and C. Carletti, *J. Prakt. Chem.*, **322**, 1063 (1980); O. Attanasi and F. Serra-Zanetti, *Synthesis*, 314 (1980); O. Attanasi and F. Serra-Zanetti, *Org. Prep. Proced. Int.*, **13**, 170 (1981); O. Attanasi, P. Filippone and F. Serra-Zanetti, *Synth. Commun.*, in press; O. Attanasi, F. Serra-Zanetti, P. Battistoni and G. Fava, *J. Prakt. Chem.*, in press; and references cited therein.
- [2] O. Attanasi, *Studi Urbinati, Fac. Farm.*, **17**, 123 (1975); O. Attanasi, P. Battistoni and G. Fava, *Synth. Commun.*, **9**, 465 (1979); O. Attanasi, *Studi Urbinati, Fac. Farm.*, **22**, 135 (1980); O. Attanasi, P. Battistoni and G. Fava, *J. Org. Chem.*, **46**, 447 (1981); O. Attanasi, P. Battistoni and G. Fava, *Org. Prep. Proced. Int.*, **15**, 1 (1983); O. Attanasi, P. Battistoni and G. Fava, submitted for publication; and references cited therein.
- [3] O. Attanasi, P. Bonifazi, E. Foresti and G. Pradella, *J. Org. Chem.*, **47**, 684 (1982).
- [4] W. Barbieri, L. Bernardi, P. Masi, L. Caglioti and G. Rosini, *Tetrahedron Letters*, 1343 (1970); L. Caglioti, E. Foresti and L. Riva di Sanseverino, *ibid.*, 1347 (1970); L. Caglioti, G. Rosini, P. Tundo and A. Vigevani, *ibid.*, 2349 (1970); W. Barbieri, L. Bernardi, P. Masi, A. Vigevani, L. Caglioti and G. Rosini, *Tetrahedron*, **27**, 5505 (1971); K. L. Zelenin, V. A. Nikitin, N. M. Anodina and Z. M. Matveeda, *Zh. Org. Khim.*, **8**, 1438 (1972), *Chem. Abstr.*, **77**, 139384 (1972); P. De Maria, F. Gasparri, L. Caglioti and M. Ghedini, *J. Chem. Soc., Perkin Trans. II*, 1922 (1973); S. Sommer, *Tetrahedron Letters*, 117 (1977); S. Sommer, *Angew. Chem., Int. Ed. Engl.*, **16**, 58 (1977); S. Sommer, *Synthesis*, 305 (1977); S. Sommer and N. Schubert, *Angew. Chem., Int. Ed. Engl.*, **18**, 696 (1979); B. F. Bonini, G. Maccagnani, G. Mazzanti, G. Rosini and E. Foresti, *J. Chem. Soc., Perkin Trans. I*, 2322 (1981); and references cited therein.
- [5] S. Bozzini, S. Gratton, A. Risaliti, A. Stener, M. Calligaris and G. Nardin, *J. Chem. Soc., Perkin Trans. I*, 1377 (1977); S. Bozzini, S. Gratton, G. Pellizer, A. Risaliti and A. Stener, *ibid.*, 869 (1979); S. Bozzini, B. Cova, S. Gratton, A. Lisini and A. Risaliti, *ibid.*, 240 (1980); S. Bozzini, S. Gratton, A. Lisini, G. Pellizer and A. Risaliti, *Tetrahedron*, **38**, 1459 (1982); and references cited therein.
- [6] L. Caglioti, P. Grasselli, F. Morlacchi and G. Rosini, *Chem. Ind. (London)*, 25 (1968); L. Caglioti, A. Dondoni and G. Rosini, *Chim. Ind. (Milano)*, **50**, 122 (1968); A. Dondoni, G. Rosini, G. Mossa and L. Caglioti, *J. Chem. Soc. (B)*, 1404 (1968); L. Caglioti and G. Rosini, *Chem. Ind. (London)*, 1093 (1969); S. Brodka and H. Simon, *Chem. Ber.*, **102**, 3647 (1969); P. M. Collins, D. Gardiner, S. Kumar and W. G. Overend, *J. Chem. Soc., Chem. Commun.*, 1433 (1970); C. E. Saks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975); S. Cacchi, M. Felici and G. Rosini, *J. Chem. Soc., Perkin Trans. I*, 1260 (1977); S. Cacchi, F. La Torre and D. Misiti, *Chim. Ind. (Milano)*, **60**, 715 (1978); G. S. Hajivarnava, W. G. Overend and N. R. Williams, *J. Chem. Soc., Perkin Trans. I*, 205 (1982); and references cited therein.
- [7a] L. Bernardi, P. Masi and G. Rosini, *Ann. Chim. (Roma)*, **63**, 601 (1973); [b] S. Brodka and H. Simon, *Ann. Chem.*, **745**, 193 (1971); [c] S. Cacchi, D. Misiti and M. Felici, *Synthesis*, 147 (1980).
- [8] H. H. Inhoffen, J. W. Buchler and P. Jager, *Fortschr. Chem. Org. Naturst.*, **26**, 284 (1968); A. Gossauer, "Die Chemie der Pyrrole", Springer-Verlag, New York, 1974; J. M. Patterson, *Synthesis*, 281 (1976); and references cited therein.
- [9] L. Caglioti and A. G. Giumanini, *Bull. Chem. Soc. Japan*, **44**, 1048 (1971); G. Rosini and A. Ranza, *J. Org. Chem.*, **36**, 1915 (1971); G. Rosini and S. Cacchi, *ibid.*, **37**, 1856 (1972); L. Caglioti, F. Gasparri, G. Paolucci, G. Rosini and P. Masi, *ibid.*, **38**, 920 (1973); G. Rosini and G. Baccolini, *ibid.*, **39**, 826 (1974); and references cited therein.
- [10] The analytical data reported in the previous paper (ref 3) for compounds **4b** and **4e** (in this work **4c** and **4n**) were casually mistaken.