July-Aug 1983

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

Orazio Attanasi*, Paola Bonifazi and Franca Bujani

Cattedra di Chimica Organica della Facoltá di Scienze, Università di Urbino, Piazza Rinascimento 6, 61029 Urbino, Italy Received September 29, 1982

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.

J. Heterocyclic Chem., 20, 1077 (1983).

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 la-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 Coper(II) Chloride Dihydrate (1:M),
Reaction Procedures and Times, Yields, and Melting Points of the Reaction Products

Azoalkene No.	1,3-dicarbonyle No.	pyrrole No.	1: M	procedure (a)	time (hours)	yields (%)	mp (°C) (b)
110.							
la	2a	4 a	8:1	Α	1	85	145-146
	2b	4b	8:1	В	1	75	134-135
	2c	4c	8:1	В	l	75	161-162
	2d	4d	8:1	С	24	65	173-174
	2e	4e	8:1	Č	1	50	144-145
	2e 2f	4f	8:1	č	8	55	212-213
*1	-		8:1	Ä	1	75	161-162
1b	2a	4g		B	1	40	148-149
	$2\mathbf{b}$	4h	8:1		1	40	108-109
	2 c	4i	8:1	В	1		
	2d	41	8:1	С	22	55	177-178
1c	2 b	4m	10:1	В	1	50	174-175
	2c	4n	10:1	В	1	75	153-154
	2d	40	10:1	С	3	55	204-205
	2a 2e	40 4p	10:1	č	1	50	215-217

The molecular ratio between (arylazo)alkenes and copper(II) chloride dihydrate (1:M), the reaction procedures and times, the yields and melting points of the reaction products are listed in the Table.

The data reported in the Table show that in several cases the 1-(arylamino)pyrrole derivatives were obtained in good yields. It is noteworthy that in the ring closure of the 1,4-adduct intermediates 3 only the ketonic carbonyl group is operative. However, in the particular case of the reactions of the (arylkazo)alkenes 1a-c with 1-phenyl-1,3-butanedione 2d the main products 4d, 4l and 4o were those derived from the ring closure by the carbonyl group at position 3.

These reactions take place under very mild conditions (magnetic stirring at room temperature), without strong acid or base, do not require expensive and difficultly available reagents, or complicated procedures. In fact, copper(II) chloride dihydrate and the 1,3-dicarbonyl compounds are commercial and low cost materials, and (arylazo)alkenes frequently are stable, useful and easily available intermediates [2,3,4-7]. Furthermore, these reactions seem to be successfully applicable to different (arylazo)alkenes and several 1,3-dicarbonyl compounds. Considering these facts, and considering that the 1-(arylamino)pyrrole derivatives are not easily synthesizable products by other known methodologies, the procedure reported in this paper represents a mild, simple and convenient method for the synthesis of these latter compounds [3,8].

These reactions probably occur by 1,4-conjugate addition (Michael-type) of the 1,3-dicarbonyl compounds to the azo-ene system of the (arylazo)alkene derivatives 3. This hypothesis is supported by some previous investigations in which the conjugate double bond system -N=N-C=C< was found frequently to have a reactivity analogous to that of other cher conjugate double bond. In fact, several azoalkenes with or without electron withdrawing groups on the azo-group are known to give (4+2)-type cycloadditions with some carbon-carbon dienophiles

heterodienophiles, providing interesting six-membered heterocyclic compounds [4]. Furthermore, some azoalkene derivatives are known to give 1,4-additions with a variety of nucleophiles, producing the respective hydrazone derivatives and the simultaneous C-functionalization which may be of great usefulness in organic synthesis [2,3,5-7]. In particular, some (arylazo)alkenes are demonstrated to undergo 1,4-conjugate addition of activated methylene compounds [3,7]. However, the above-mentioned reactions cannot always be so immediately extended and generalized to all azoalkene derivatives known, mainly because their different stability degree: some of these compounds may not be very stable and may be difficult to preserve, while others are stable and easily available products [2,3,5-7,9].

When a ketonic carbonyl group is present, the 1,4-adducts 3 give a ring closure followed by water elimination, affording the relative pyrrole derivatives 4a-p, instead of the dihydropyridazine derivative, as erroneously reported by Brodka et al., and unequivocally demonstrated in our previous paper [3,7a-b].

As above mentioned, in all cases the amounts of copper(II) chloride dihydrate were decreased to much less than the stoichiometric amounts (see Table and Experimental). This fact supports the hypothesis of a catalytic role for the copper(II) ions [1,3]. Very likely, the easy reactions observed can be ascribed to the higher reactivity between the (arylazo)alkene derivatives and 1,3-dicarbonyl compounds when these reagents are present in the form of organometallic complexes rather than in the form of pure reagents. In fact, it is known that these compounds can form complexes and chelates with several metal ions, and in particular with copper(II) ions [1,3]. After the reaction the metal ions would regenerate in the original form and would again become operative until the reaction was complete.

In conclusion, it can be hypothesized that a thermodynamic and/or kinetic effect would drive these reactions to completion. 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 la-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)azo]-cyclohexene 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 (phenaylazo)stilbene 1a, 1.68 mmoles of (phenylazo)diphenylpropene 1b or 2.16 mmoles of [(p-nitrophenyl)azo]cyclohexene 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-carbethoxy-5-methylpyrrole 4c, 1-phenylamino-2,3-diphenyl-4-oxo-4,5,6,7-tetrahydroindole 4f, 1-phenyl-4-oxo-4,5,6,7-tetrahydroindole 4

amino-2-benzyl-3-phenyl-4-acetyl-5-methylpyrrole **4g** and 1-(*p*-nitrophenylamino)-2-methyl-3-carbethoxy-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 $C_{25}H_{22}N_2O_2$: 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 $C_{30}H_{24}N_2O$: 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=0), 1600 cm⁻¹ (aromatic); 'H nmr (deuteriochloroform, TMS): δ 6.30-8.15 (m).

Anal. Calcd. for $C_{35}H_{26}N_2O$: 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 $C_{26}H_{24}N_2O_2$: 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-carbethoxy-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 $C_{27}H_{26}N_2O_2$: 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 41.

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 (2OH, m).

Anal. Calcd. for $C_{31}H_{26}N_2O$: 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 $^{-1}$ (NO $_2$); 1 H 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 $C_{17}H_{19}N_3O_4$: 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 40.

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.

Acknowledgment.

This work was supported by the financial assistance from the Consiglio Nazionale delle Richerche (Roma). The authors gratefully acknowledge Dr. Stefania Santeusanio for collaboration in this work.

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 publica-
- [3] O. Attanasi, P. Bonifazi, E. Foresti and G. Pradella, J. Org. Chem., 47, 684 (1982).

tion; and references cited therein.

[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. Gasparrini, 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 therin. [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. Gasparrini, 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.