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Straightforward Entry into 5-Hydroxy-1-aminopyrrolines and the Corresponding Pyrroles from 1,2-Diaza-1,3-butadienes

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The synthesis of 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives and 5-unsubstituted-1-aminopyrrole-3-carboxylic acid derivatives from 1,2-diaza-1,3-butadienes and aldehydes is presented. These domino reactions offer the advantage of executing multistep transformation without intermediate workup procedures. The stereoselectivity of ring closure to 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives and phenyl transposition to 2,3-diphenyl-1-aminopyrrole-3-carboxylic acid derivatives are also studied.

1,2-Diaza-1,3-butadienes have attracted increasing attention because of their potential use in organic synthesis.[1−5] In previous papers, we reported the synthesis of 2-hydroxy-1-aminopyrrolines and 2-substituted-1-aminopyrroles by reaction of 1,2-diaza-1,3-butadienes with β-coactivated methylene or methyne carbonyl compounds.[3,6]

Here, we report the first synthesis of 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives and 5-unsubstituted-1-aminopyrrole-3-carboxylic acid derivatives by reaction of the same starting materials with methylene or methyne compounds bearing in the α-position only one aldehyde carbonyl group as such or generated in situ from the relevant acetal derivatives.[7] The reaction showed complete stereoselectivity and allowed us to obtain only H_4,H_5-*trans*-5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives. By using diphenylacetaldehyde, a transposition of phenyl group to obtain 2,3-diphenyl-1-aminopyrrole-3-carboxylic acid derivatives was also observed. Moreover, the reaction successfully occurred also with β-ester or β-keto aldehydes generated in situ from the relevant acetal derivatives.[7] It is noteworthy that these reactions were catalyzed by basic resins, making the workup procedures of the reaction mixtures very simple and environmentally friendly.

The synthesis of 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives **5a**−**i** starting from 1,2-diaza-1,3-butadienes **1a**−**f** and phenylacetaldehyde (**2a**) or diphenylacetaldehyde (**2b**) by catalysis of sodium methoxide is illustrated in Scheme 1. The reaction took place by a nucleophilic attack of the carbon atom in the α-position of the aldehyde at the terminal carbon of heterodiene system to give an adduct intermediate, not isolable, that promptly afforded 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives by an intramolecular cyclization. The five-membered ring closure is substantiated by several papers presented by our research group.[3] This cyclization, arising from the attack of hydrazone nitrogen at the carbonyl function, showed complete stereoselectivity, and only H_4,H_5-*trans*-5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives were detected. The stereochemistry was supported by NMR studies: in fact, in compounds **5a**−**c** for H_4, coupling constants $J_{4,5} = 7.6$ Hz were observed, typical for two protons in the anti position in pyrroline ring,[8] while for H_5 only a broad singlet was detected probably due to the presence of hydroxy group. By treatment with a catalytic amount of copper(II) chloride dihydrate or Amberlyst 15 (H) or trifluoroacetic

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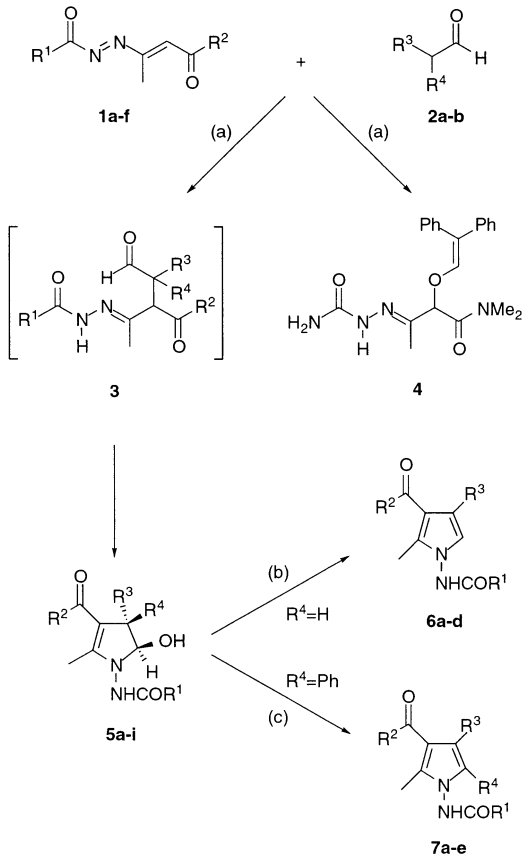
SCHEME 1[a]



[a] Reagents and conditions: (a) CH_3ONa (cat.)/THF/rt, 0.5 h; (b) Amberlyst 15 (H)/THF/rt, 0.5 h or $CuCl_2 \cdot 2H_2O$/THF/rt, 0.5 h or TFA/rt, 0.5 h; (c) $Cu(OTf)_2$/THF/rt/1 h.

acid, H_4,H_5-*trans*-5-hydroxy-1-aminopyrrolines-3-carboxylic acid derivatives **5a**−**d** easily afforded 5-unsubstituted-1-aminopyrrole-3-carboxylic acid derivatives **6a**−**d** through a water molecule elimination. This last process, in some cases, took place in the NMR tube, and it was not possible to determine melting points of H_4,H_5-*trans*-5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives **5a**−**d**,**j**−**k**. In fact, the heating of these compounds **6a**−**f** gave a partial transformation to **6a**−**f**. When 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives **5e**−**i** were treated with copper(II) trifluoromethanesulfonate, the formation of 2,3-diphenylaminopyrrole-3-carboxylic acid derivatives **7a**−**e** was observed. These last compounds arise from phenyl transposition and loss of a water molecule (Scheme 1, Table 1). Presumably, the interation of Lewis acid with the alcohol moiety facilitates the formation of the carbocation and the subsequent 1,2-phenyl shift to give a more stable intermediate.[9]

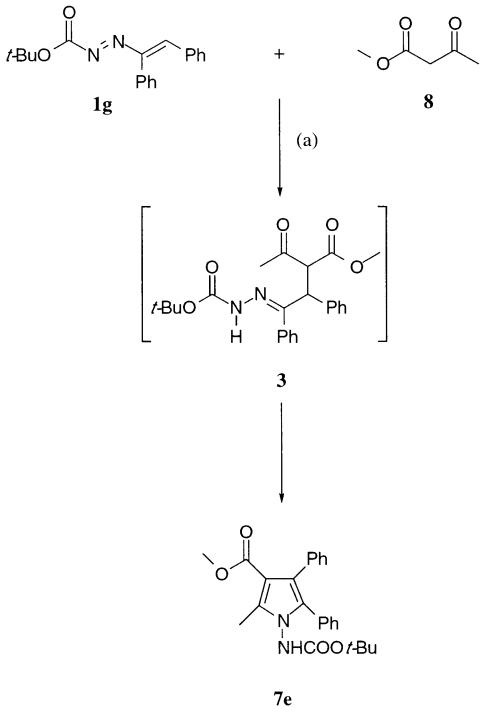
The structures of 2,3-diphenylaminopyrrole-3-carboxylic acid derivatives **7a**−**e** were supported by spectroscopic evidence and unequivocally confirmed by comparison of 2,3-diphenylaminopyrrole-3-carboxylic acid derivative **7e** with the same 1-aminopyrrole derivative obtained by reaction of azoalkene **1g** with methyl acetoacetate (**8**) in tetraydrofuran in the presence of a catalytic amount of copper(II) chloride dihydrate[10] (Scheme 2).

TABLE 1. Yields of 5-Hydroxy-1-aminopyrroline-3-carboxylic Acid Derivatives 5a−i, 5-Unsubstituted-1-aminopyrrole-3-carboxylic Acid Derivatives 6a−d, and 2,3-Diphenylaminopyrrole-3-carboxylic Acid Derivatives 7a−e[a]

entries	5	yield (%)	6	yield (%)	7	yield (%)
1a + **2a**	**5a**	44	**6a**	89		
1b + **2a**	**5b**	39	**6b**	85		
1c + **2a**	**5c**	42	**6c**	91		
1f + **2a**	**5d**	57	**6d**	79		
1a + **2b**	**5e**	46			**7a**	87
1b + **2b**	**5f**	67			**7b**	76
1d + **2b**	**5g**	42			**7c**	83
1e + **2b**	**5h**	61			**7d**	92
1f + **2b**	**5i**	74			**7e**	87

[a] Yield of pure isolated products.

SCHEME 2[a]



[a] Reagents and conditions: (a) $CuCl_2 \cdot 2H_2O$ (cat.)/THF/rt, 1 h.

When 1,2-diaza-1,3-butadiene **1c** was reacted with diphenylacetaldehyde (**2b**) in the presence of a catalytic amount of sodium methoxide, only product **4** was recovered. This compound derives from nucleophilic attack by oxygen of the enolic form of diphenylacetaldehyde to the azoene system of 1,2-diaza-1,3-butadienes. The same addition products were observed in very small yields in all reactions of 1,2-diaza-1,3-butadienes **1a**,**b** with diphenylacetaldehyde (**2b**) (Scheme 1).

Then, we decided to extend the investigation concerning conjugate addition to 1,2-diaza-1,3-butadienes using

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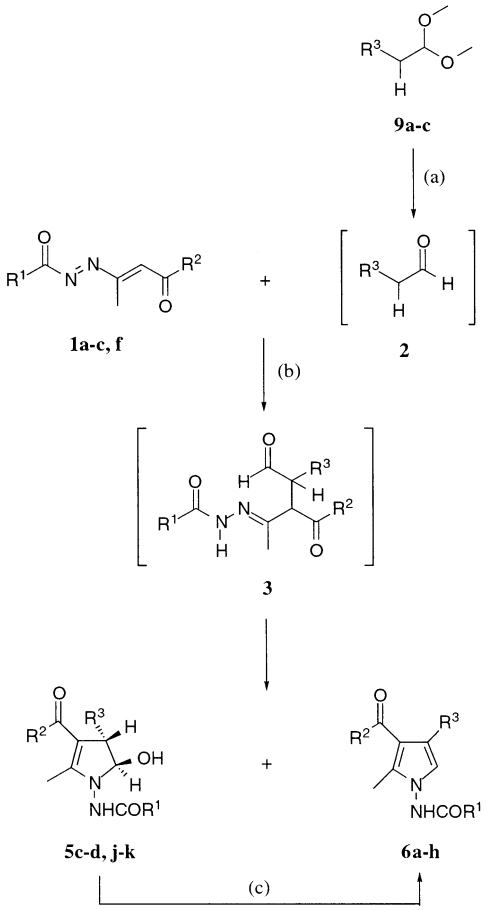
SCHEME 3[a]



1a: R^1=NH_2, R^2=OMe
1b: R^1=NH_2, R^2=OEt
1c: R^1=NH_2, R^2=NMe_2
1f: R^1=O*t*-Bu, R^2=OMe
9a: R^3=Ph
9b: R^3=COMe
9c: R^3=CO_2Me

[a] Reagents and conditions: (a) Dowex 50W/H_2O/rt, 24 h or Amberlyst 15 (H)/CH_3COCH_3−H_2O/rt, 12 h; (b) Duolite A 102/rt, 10 h; (c) Amberlyst 15 (H)/THF/rt, 0.5 h or $CuCl_2$·$2H_2O$/THF/rt, 0.5 h or TFA/rt, 0.5 h.

acetal derivatives as precursor of aldehydes not commercially available. Among the methods reported in the literature for the generation in situ of aldehydes from the relevant acetal we used Amberlyst 15 (H) in acetone−water mixture in the case of **9a**,**b**[7] or Dowex 50W in water in the case of **9c**. Phenylacetaldehyde, acetylacetaldehyde, and methyl-3-oxopropanoate generated in situ from the relevant acetal derivatives **9a**−**c**, after filtration of used resins and addition of Duolite A 102, were reacted with 1,2-diaza-1,3-butadienes **1a**−**c**,**f**. Under these reaction conditions, the direct formation of 5-unsubstituted-1-aminopyrrole-3-carboxylic acid derivatives **6a**−**h** was observed. In the case of the reaction between **1a**−**c**,**f** and **9a**,**b**, it was possible to isolate H_4,H_5-*trans*-5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives **5c**−**d**,**j**−**k**. Treatment of these substrates in tetrahydrofuran with Amberlyst 15 (H) or copper(II) chloride dihydrate[6] or trifluoroacetic acid furnished the corresponding 5-unsubstituted-1-aminopyrrole-3-carboxylic acid derivatives **6c**−**f** (Scheme 3, Table 2).

In conclusion, this work offers a simple and convenient access to new classes of 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives and 5-unsubstituted-1-aminopyrrole-3-carboxylic acid derivatives from easily accessible starting materials, which are of great interest both as products and intermediates in organic, biological, pharmaceutical, analytical and agricultural chemistry.[11] The stereoselectivity of ring closure to 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives and phenyl transposition to 2,3-diphenyl-1-aminopyrrole-3-carboxylic acid derivatives is also described.

TABLE 2. Yields of 5-Hydroxy-1-aminopyrroline-3-carboxylic Acid Derivatives 5c−k and 5-Unsubstituted-1-aminopyrrole-3-carboxylic Acid Derivatives 6a−h

entries	5	yield (%)	6	yield (%)
1a + **9a**			**6a**	39[a]
1b + **9a**			**6b**	49[a]
1c + **9a**	**5c**	67[a]	**6c**	5[a]
			6c	91[b]
1f + **9a**	**5d**	37[a]	**6d**	7[a]
			6d	79[b]
1a + **9b**	**5j**	45[a]	**6e**	8[a]
			6e	85[b]
1b + **9b**	**5k**	35[a]	**6f**	6[a]
			6f	87[b]
1a + **9c**			**6g**	89[a]
1b + **9c**			**6h**	37[a]

[a] Yield of pure isolated products starting from **1**+**9**. [b] Yield of pure isolated products starting from **5**.

Experimental Section

General Methods. Phenylacetaldehyde, diphenylacetaldehyde, acetylacetaldehyde dimethyl acetal, methyl 3,3-dimethoxypropionate, phenylacetaldehyde dimethyl acetal, methyl acetoacetate, sodium methoxide (CH_3ONa), trifluoroacetic acid (TFA), Amberlyst 15 (H), Dowex 50W, Duolite A 102, copper(II) chloride dihydrate ($CuCl_2$·$2H_2O$), and copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) were commercial materials and were used without further purification. Solvents were purchased and were used without further purification with the exception of THF, which was distilled from sodium hydroxide. 1,2-Diaza-1,3-butadienes **1a**−**g** were synthesized as standard *E*/*Z* isomeric mixtures according to previously reported procedures.[12,13] Melting points were determined in open capillary tubes and are uncorrected. IR−FT spectra were obtained as Nujol mulls. Mass spectra were made at an ionizing voltage of 70 eV. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Chemical shifts (δ_H) are reported relative to TMS as internal standard. All coupling constants (*J*) are given in Hz. Chemical shifts (δ_C) are reported relative to DMSO-d_6 as internal standard in a broad band decoupled mode; all the NH and OH exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin-layer chromatography and silica gel 35−70 μm for column chromatography. All new compounds showed satisfactory elemental analysis (C ±0.35; H ±0.30, N ±0.30).

General Procedure for the Synthesis of 5-Hydroxy-1-aminopyrroline-3-carboxylic Acid Derivatives 5a−i and

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2-{3-(Dimethylamino)-1-methyl-3-oxo-2-[(2,2-diphenylvinyl)oxy)]}-hydrazine-1-carboxamide (4) Starting from 1a−f and 2a,b. To a magnetically stirred solution of 1,2-diaza-1,3-butadienes **1a**−**f** (1 mmol) and CH_3ONa (0.2 mmol) in THF (20 mL) were added aldehydes **2a**,**b** (1 mmol). The reaction was allowed to stand at room temperature until the complete disappearance of **1a**−**f** (0.5 h, monitored by TLC). The reaction mixture was concentrated directly under reduced pressure. Products **4** (38%) and **5a**−**i** (see Table 1) were isolated by chromatography on silica gel column with cyclohexane−ethyl acetate (10:90 v/v) and then purified by crystallization from diethyl ether and petroleum ether (bp 40−60 °C).

General Procedure for the Synthesis of 5-Hydroxy-1-aminopyrroline-3-carboxylic Acid Derivatives 5c−d,j−k and 5-Unsubstituted-1-aminopyrrole-3-carboxylic Acid Derivatives 6a−h Starting from 1a−c,f and 9a−c. To a magnetically stirred solution of acetal **9a**,**b** (2 mmol) in acetone (8 mL) and H_2O (0.12 mL) was added Amberlyst 15 (H) (0.08 g), and the mixture was stirred at rt for 12 h,[7] while to a solution of **9c** (2 mmol) in H_2O (10 mL) was added Dowex 50W (0.8 g) and the mixture stirred at rt for 24 h. To this resulting solution, after filtration of the ion-exchange resin, were added 1,2-diaza-1,3-butadienes **1a**−**c**,**f** (1 mmol) and Duolite A 102 (0.5 mmol). The reaction was allowed to stand at room temperature until the complete disappearance of **1a**−**c**,**f** (10 h, monitored by TLC). The solution was filtered and concentrated under reduced pressure, and the mixture residue was dissolved in ethyl acetate, dried over Na_2SO_4, and evaporated. Products **5c**−**d**,**j**−**k** and **6a**−**h** (see Table 2) were obtained by chromatography on silica gel column with cyclohexane−ethyl acetate (10:90 v/v) and then purified by crystallization from diethyl ether and petroleum ether (bp 40−60 °C).

General Procedure for the Synthesis of 5-Unsubstituted-1-aminopyrrole-3-carboxylic Acid Derivatives 6a−f Starting from 5-Hydroxy-1-aminopyrroline-3-carboxylic Acid Derivatives 5a−d,j−k. To a magnetically stirred solution of 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives **5a**−**d**,**j**−**k** (1 mmol) in THF (10 mL) was added $CuCl_2 \cdot 2H_2O$ (0.1 mmol), Amberlyst 15 (H) (0.8 g), or TFA (1.0 mmol). The reaction was allowed to stand at room temperature until the complete disappearance of **5a**−**d**,**j**−**k** (0.5 h, monitored by TLC). After evaporation of the solvent under reduced pressure, the crude mixture was solved in ethyl acetate and washed with brine, and the organic layer was dried over Na_2SO_4, filtered, and evaporated. Compounds **6a**−**f** (see Table 2) were obtained after crystallization from diethyl ether and petroleum ether (bp 40−60 °C).

2-{3-(Dimethylamino)-1-methyl-3-oxo-2-[(2,2-diphenylvinyl)oxy)]}-hydrazine-1-carboxamide (4): mp 150−153 °C; ^{1}H NMR (DMSO-d_6) δ 1.76 (s, 3 H), 2.84 (s, 3 H), 2.95 (s, 3 H), 5.44 (s, 1 H), 6.31 (bs, 2 H), 6.67 (s, 1 H), 7.10−7.40 (m, 10 H), 9.40 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 12.3, 35.4, 36.5, 82.1, 119.8, 126.4, 126.5, 127.7, 127.9, 128.4, 129.6, 137.2, 139.8, 142.9, 143.8, 156.9, 166.6; IR 3431, 3284, 3235, 1685, 1651 cm^{-1}; MS *m*/*z* 380 (M^+, 1), 362 (15), 318 (20), 196 (18), 167 (100). Anal. Calcd for $C_{21}H_{24}N_4O_3$: C, 66.30; H, 6.36; N, 14.73. Found: C, 66.41; H, 6.32; N, 14.81.

Methyl (4*S,5*R**)-1-[(aminocarbonyl)amino]-5-hydroxy-2-methyl-4-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (5a):** ^{1}H NMR (DMSO-d_6) δ 2.14 (d, J = 1.2 Hz, 3 H), 3.31 (s, 3 H), 3.69 (dq, J = 3.6 Hz, J = 1.2 Hz 1 H), 4.65 (bs, 1 H), 5.98 (bs, 2 H), 6.50 (d, J = 7.2 Hz, 1 H), 7.10−7.30 (m, 5 H), 8.16 (bs, 1 H); ^{13}C NMR (DMSO-d_6) δ 11.8, 50.0, 54.3, 93.9, 99.2, 126.2, 127.5, 128.2, 143.4, 158.2, 159.4, 165.7; IR 3328, 3201, 1705, 1681 cm^{-1}; MS *m*/*z* 291 (M^+, 6), 273 (100). Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.69; H, 5.81; N, 14.37.

Methyl 1-[(aminocarbonyl)amino]-2-methyl-4-phenyl-1*H*-pyrrole-3-carboxylate (6a): mp 192−195 °C; ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3 H), 3.57 (s, 3 H), 6.28 (s, 2 H), 6.75 (s, 1 H), 7.16−7.32 (m, 5 H), 9.37 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 10.5, 50.3, 107.6, 121.5, 122.8, 125.9, 127.5, 128.6, 135.1, 137.4, 157.2, 165.0; IR 3421, 3304, 3201, 1710, 1675 cm^{-1}; MS *m*/*z* 273 (M^+, 100). Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.59; H, 5.45; N, 15.31.

General Procedure for the Synthesis of 2,3-Diphenylaminopyrrole-3-carboxylic Acid Derivatives 7a−e Starting from 5e−i. To a magnetically stirred solution of 5-hydroxy-1-aminopyrroline-3-carboxylic acid derivatives **5e**−**i** (1 mmol) in THF (10 mL) was added $Cu(OTf)_2$ (0.1 mmol). The reaction was allowed to stand at room temperature until the complete disappearance of **5e**−**i** (1.0 h, monitored by TLC). After the evaporation of the solvent under reduced pressure, the crude mixture was solved in ethyl acetate and washed with brine, and the organic layer was dried over Na_2SO_4, filtered, and evaporated. Compounds **7a**−**e** (see Table 1) were purified by crystallization from diethyl ether and petroleum ether (bp 40−60 °C).

Methyl 1-[(aminocarbonyl)amino]-2-methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (7a): mp 215−217 °C; ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3 H), 3.50 (s, 3 H), 6.23 (s, 2 H), 7.01−7.22 (m, 10 H), 9.20 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 11.7, 51.2, 109.0, 121.1, 126.4, 127.7, 127.8, 128.3, 130.9, 131.0, 131.1, 131.9, 135.9, 137.6, 157.6, 165.5; IR 3405, 3263, 3197, 1719, 1676 cm^{-1}; MS *m*/*z* 350 (M^+ + 1, 23), 349 (M^+, 100). Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.89; H, 5.41; N, 12.07.

Procedure for the Synthesis of Methyl 1-[(*tert*-Butoxycarbonyl)amino]-2-methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (7e) Starting from 1g and 8.[10] Copper(II) chloride dihydrate (0.1 mmol) dissolved in THF (5 mL) was added to a solution of azoalkene **1g** (1 mmol) in methyl acetoacetate (**8**) (15 mL). The mixture was magnetically stirred at room temperature for 1 h until the reaction was completed (monitored by TLC). The reaction mixture was poured into diethyl ether and washed several times with saturated aqueous Na_2CO_3 and then with brine. The organic layer was dried with anhydrous Na_2SO_4, and after evaporation under reduced pressure, it provided the relevant 1-amminopyrrole derivative **7e** (35%).

Methyl 1-[(*tert*-butoxycarbonyl)amino]-2-methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (7e): mp 180−182 °C; ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 9 H), 2.35 (s, 3 H), 3.50 (s, 3 H), 7.00−7.24 (m, 10 H), 10.30 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 10.8, 27.8, 50.5, 80.7, 108.5, 120.7, 125.8, 127.0, 127.3, 127.7, 129.8, 130.1, 130.2, 130.9, 134.8, 136.0, 154.2, 164.5; IR 3325, 3258, 1735, 1683 cm^{-1}; MS *m*/*z* 407 (M^++1, 2), 406 (M^+, 24), 349 (23), 350 (100). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.99; H, 6.37; N, 6.95.

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Supporting Information Available: Product characterization data, ^{1}H and ^{13}C NMR peak listings for **5b**−**k**, **6b**−**h**, and **7b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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