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Modular One-Pot Synthesis of Tetrasubstituted Pyrroles from α-(Alkylideneamino)nitriles‡

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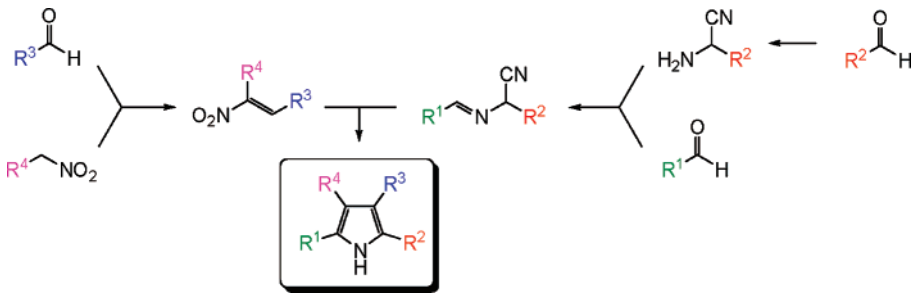
Received March 1, 2007



2,3,4,5-Tetrasubstituted pyrroles have been prepared with high regioselectivity by a formal cycloaddition of α-(alkylideneamino)nitriles and nitroolefins followed by elimination of HCN and HNO_2. The reaction allows the convergent construction of the pyrrole ring in four steps from a nitroalkane and three aldehydes.

Introduction

Pyrroles are found as key structural elements in a vast number of natural products, for example, the marine and terrestrial pyrrole alkaloids, pyrrole-imidazole alkaloids, and the ubiquitous porphyrins.[1−7] In addition, pyrrole derivatives have found broad application in medicine and materials science.[8−13] A well-known example is the top-selling drug atorvastatin (Lipitor), which is applied as an antihyperlipidemic agent.[14] Consequently, a large number of synthetic methods for the construction of the pyrrole ring have been developed, for example, the Knorr,[15] Paal−Knorr,[16,17] and Hantzsch syntheses,[18] [3 + 2]-cycloadditions,[19−21] multicomponent reactions,[22−24] and ring contractions[25] or cyclizations.[26−29] Here, we describe facile access to highly

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‡ Dedicated to Prof. Herbert Waldmann on the occasion of his 50th birthday.

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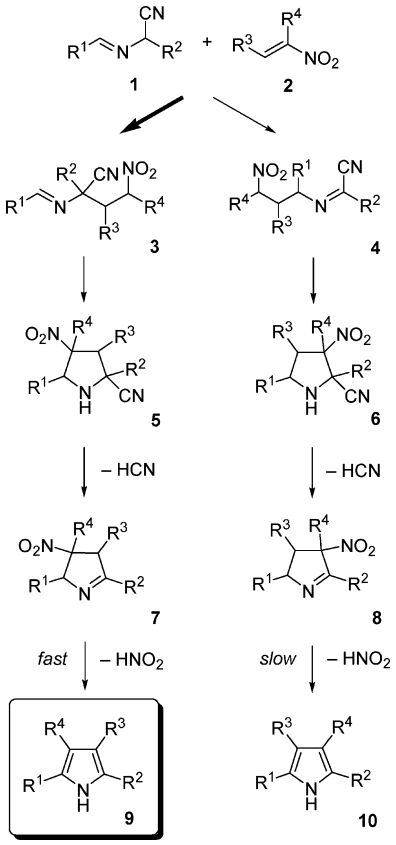
10.1021/jo070426x CCC: $37.00 © 2007 American Chemical Society
Published on Web 08/22/2007

SCHEME 1. General Reaction Course for the Formation of Pyrroles



substituted pyrroles by addition of α-(alkylideneamino)nitriles to α,β-unsaturated nitro compounds under basic conditions.

Results and Discussion

α-(Alkylideneamino)nitriles (**1**) can be readily obtained by condensation of Strecker products derived from ammonia with aldehydes.[30] The extended conjugation of their anions makes them CH-acidic, so that even guanidine bases such as TBD or amidine bases such as DBU suffice for their deprotonation. We have recently demonstrated that the conjugate addition of deprotonated α-(alkylideneamino)nitriles to α,β-unsaturated ketones or esters[31] can be used as the key step for the preparation of highly substituted pyrrolidines[32,33] and of γ-amino acid esters and γ-lactams.[34] In some cases, cyclization of the intermediate enolates by means of a 5-*endo-trig* process cannot be prevented.[35−37] A similar reaction sequence, in which the electrophile contains a potential leaving group, should allow the preparation of polysubstituted pyrroles. Indeed, we found that the reaction of α-(alkylideneamino)nitriles (**1**) with nitroolefins (**2**) under basic conditions directly furnishes 2,3,4,5-tetrasubstituted pyrroles (**9a**−**n**) (Scheme 1, Table 3).

The course of the reaction presumably involves the conjugate addition of the stabilized 2-azaallyl anion to the Michael acceptor followed by nucleophilic attack of the resulting nitronate to the imine carbon under formation of a 2-cyano-4-nitropyrrolidine **5**.[31,38] Alternatively, compounds **5** could be formed by a 1,3-dipolar cycloaddition of an azomethine ylide equivalent derived from **1**.[38−40] Unfortunately, the regioisomeric 2-cyano-3-nitropyrrolidines **6** may be formed as well. Elimination of HCN from compounds **5** and **6** leads to the regioisomeric nitropyrrolines **7** and **8**, respectively, which exhibit different behavior under the basic reaction conditions. In the 4-nitro-1-pyrrolines **7**, the potential leaving group is located in β-position to the acidifying imine moiety and they readily eliminate HNO_2 under formation of the pyrroles **9**. In contrast, the 3-nitro-1-pyrrolines **8** are more persistent, and elimination of HNO_2 occurs only under more drastic conditions, leading to the regioisomeric pyrroles **10**. Due to their different polarity, the chromatographic separation of compounds **8** and **9** is much easier than the separation of pyrroles **9** and **10**. Therefore, it is advisable to control the reaction conditions so that only the major addition product is converted to the pyrrole. As the choice of base, solvent, and temperature may also influence the regioselectivity of the primary addition reaction, it is difficult to distinguish between these effects only on the basis of yield and isomeric ratio of the pyrrole fraction. When α-(alkylideneamino)nitrile **1a**, nitroolefin **2a**, and 2 equiv of KO^{t}Bu were heated in THF to 60 °C, a mixture of the regioisomeric pyrroles **9a** and **10a** in a ratio of 1.6:1 was isolated in 19% yield (entry 2, Table 1). We tested several bases, solvents, and temperatures to optimize yield as well as isomeric ratio and found out that isomerically pure **9a** (51% isolated yield) can be obtained with Cs_2CO_3 in refluxing THF (see Tables 1 and 3).

Reaction of imine **1b** and nitroolefin **2a** under these conditions furnished pure pyrrole **9g** in 36% yield along with the 3-nitro-1-pyrroline **8g** (31%), the relative configuration of which was assigned by NOE experiments.

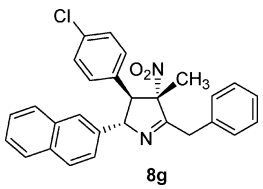


FIGURE 1. Isolated side product.

A different side product was obtained when **1b** was reacted with 1-nitrocyclohexene (**2g**) to pyrrole **9l**. Examination of the product by 2D NMR spectroscopy revealed the formation of the 4-amino-5,6,7,8-tetrahydroisoquinoline **11** (17% yield). This compound was presumably formed by attack of the benzylic

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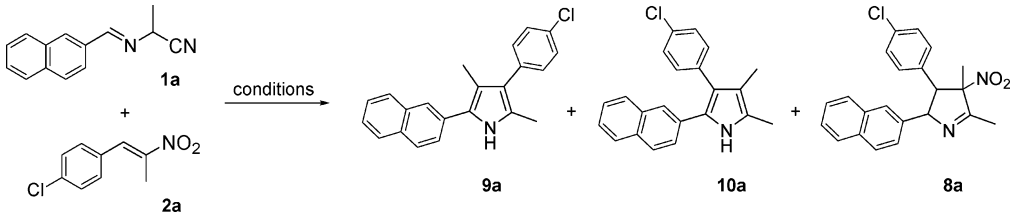
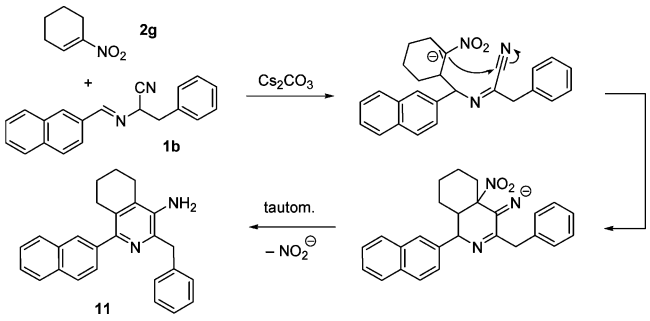
TABLE 1. Optimization of Reaction Conditions



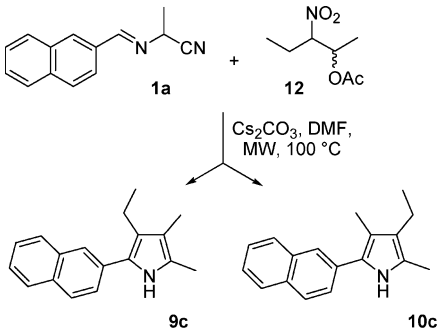
entry	base (equiv)	solvent	temp, °C	time, h	product ratio[a] **9a:10a:8a**	% **9a**[a]
1	KO^{t}Bu (1.05)	THF	60	120	1:0:0.7	33
2	KO^{t}Bu (2.7)	THF	60	16.5	1:0.9:0	19[b]
3	KO^{t}Bu (2)	THF	60	3.5	1:0:0	24[c]
4	Me_4NOH (2)	THF/MeOH 2:1	25	18	1:0.5:0	17
5	DBU (2)	THF	25	18	1:0:1.7	23
6	KO^{t}Bu (2)	THF	25	18	nd	nd[d]
7	KOH (2)	THF	25	18	nd	nd[e]
8	BaO (2)	THF	25	18	nd	nd[f]
9	Cs_2CO_3 (2)	THF	25	18	1:0:0.2	48
10	Cs_2CO_3 (2)	MeCN	25	23	1:0:0.6	38
11	Cs_2CO_3 (2)	DMF	25	23	1:0:0.6	39
12	Cs_2CO_3 (2)	^{i}PrOH/THF 3.5:1	25	23	nd	nd[d]
13	Cs_2CO_3 (2)	dioxane	25	23	nd	nd[d]
14	Cs_2CO_3 (2)	CH_2Cl_2	25	23	nd	nd[d]
15	Cs_2CO_3 (2)	toluene	25	23	nd	nd[d]
16	Cs_2CO_3 (2)	^{t}BuOMe	25	23	nd	nd[d]
17	Cs_2CO_3 (2)	THF	60	8.5	1:0:0.15	58
18	Cs_2CO_3 (2), Bu_4NHSO_4 (0.1)	THF	60/25	7.5/16	1:0.56:0.36	39
19	Cs_2CO_3 (2), Bu_4NHSO_4 (0.1)	THF	25	23.5	1:0:1.29	24
20	TBD (2)	THF	25	6	1:0.65:1.15	26
21	TBD (2)	MeOH	25	6	1:0:1.45	22
22	TBD (2)	CH_2Cl_2	25	6	1:0.18:0.49	50

[a] Determined by ^{1}H NMR spectroscopy (percentage: relative integral of 5-CH_3 signal of **9a** compared to all aromatic protons). [b] Combined isolated yield. [c] Temperature was raised to 60 °C before the base was added. [d] Slow reaction with formation of side products. [e] Formation of side products. [f] No conversion.

SCHEME 2. Formation of Side Product 11



SCHEME 3. Pyrroles from *β*-Acetoxynitroalkanes



9c/**10c** 3.75:1, 37% combined yield

center of the 2-azaallyl anion on the *β*-carbon of the Michael acceptor and subsequent nucleophilic attack of the resulting nitronate on the nitrile carbon (Scheme 2).

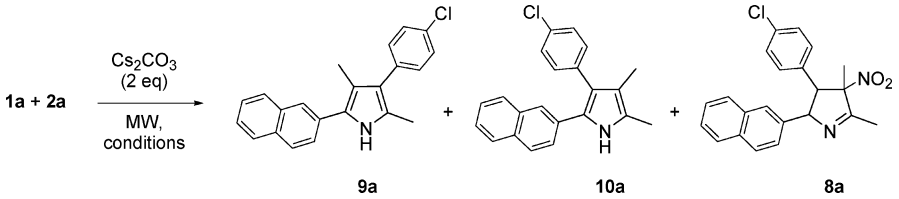
So far, we could not identify conditions under which compound **11** can be obtained as the major product. Microwave irradiation increases the rate of the pyrrole synthesis compared to conventional heating (complete conversion within 2 min). However, the conditions had to be adapted to avoid formation of the regioisomeric pyrroles. The best results were obtained with DMF as the solvent at 100 °C (entry 8, Table 2). Again, complete regioselectivity on the stage of the pyrrole was observed with Cs_2CO_3 as a base.[41]

Whereas the majority of the investigated nitroolefins could be converted to isomerically pure pyrroles (Table 3), use of the 4-cyanophenyl-substituted acceptor **2e** led to the formation of isomeric mixtures (entries 6 and 10). A rationale for this behavior may be the enhanced acidity of H-4 in the corresponding 3-nitro-1-pyrrolines (**8**), which accelerates the elimination of HNO_2 to form pyrroles **10**.

Apart from nitroolefins, *β*-acetoxynitroalkanes can serve as alternative electrophiles,[42] although the resulting regioselectivities are lower. For instance, the reaction of **1a** with acetate **12**

(41) While both conventional and microwave heating furnished crude pyrroles with surprisingly clean NMR spectra, TLC also indicated the formation of undefined polar (polymeric?) side products in all cases. This largely accounts for the deviation of the combined yields of compounds **8** and **9** from unity.

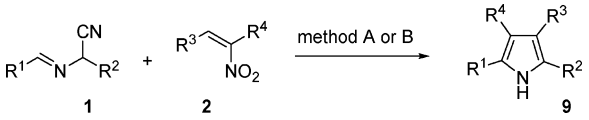
TABLE 2. Optimization of Reaction under Microwave Heating



entry	solvent	temp, °C	*t* (run), min	*t* (hold), min	product ratio[a] **9a**:**10a**:**8a**	% **9a**[a]
1	THF	67	1	2	nd	nd[b]
2	CH_3CN	81	2	2	nd	nd[b,c]
3	EtOH	79	2	2	nd	nd[b,c]
5	DMF	150	2	2	nd	nd[b,d]
6	DMF	150	2	2	1:0.22:0	39
7	DMF	100	2	2	1:0:0.4	44
8	DMF	100	2	2	1:0:0.34	54[e]

[a] Determined by ^{1}H NMR spectroscopy (percentage = relative integral of CH_3 signal at 2.34 ppm compared to all aromatic protons). [b] Formation of **9a** observed by TLC. [c] Complete conversion, formation of side products. [d] Complete conversion, formation of **9a** and one side product. [e] Isolated yield.

TABLE 3. Preparation of Pyrroles 9



entry	imine	R^1	R^2	nitroolefin	R^3	R^4	pyrrole	method[a]	yield, %
1	**1a**	2-Naph	Me	**2a**	4-Cl-C_6H_4	Me	**9a**	A	51
2	**1a**	2-Naph	Me	**2a**	4-Cl-C_6H_4	Me	**9a**	B	54
3	**1a**	2-Naph	Me	**2b**	3,4-$(MeO)_2C_6H_3$	Me	**9b**	B	40
4	**1a**	2-Naph	Me	**2c**	Me	Et	**9c**	B	33
5	**1a**	2-Naph	Me	**2d**	Me	*n*-Pent	**9d**	B	34
6	**1a**	2-Naph	Me	**2e**	4-CN-C_6H_4	Et	**9e**/**10e** (7:1)	B	56
7	**1a**	2-Naph	Me	**2f**	Ph	Ph	**9f**	B	34
8	**1b**	2-Naph	Bn	**2a**	4-Cl-C_6H_4	Me	**9g**	A	36
9	**1c**	3,4-$(MeO)_2C_6H_3$	Bn	**2a**	4-Cl-C_6H_4	Me	**9h**	A	43
10	**1d**	3,4-$(MeO)_2C_6H_3$	Ph	**2e**	4-CN-C_6H_4	Et	**9i**/**10i** (3:1)	B	42
11	**1d**	3,4-$(MeO)_2C_6H_3$	Ph	**2f**	Ph	Ph	**9j**	B	31
12	**1a**	2-Naph	Me	**2g**	-$(CH_2)_4$-		**9k**	A	46
13	**1b**	2-Naph	Bn	**2g**	-$(CH_2)_4$-		**9l**	A	37
14	**1c**	3,4-$(MeO)_2C_6H_3$	Bn	**2g**	-$(CH_2)_4$-		**9m**	A	38
15	**1c**	3,4-$(MeO)_2C_6H_3$	Bn	**2g**	-$(CH_2)_4$-		**9m**	B	51
16	**1d**	3,4-$(MeO)_2C_6H_3$	Ph	**2g**	-$(CH_2)_4$-		**9n**	A	33
17	**1d**	3,4-$(MeO)_2C_6H_3$	Ph	**2g**	-$(CH_2)_4$-		**9n**	B	43

[a] Method A: 2 equiv of Cs_2CO_3, THF, reflux. Method B: 2 equiv of Cs_2CO_3, DMF, microwave heating, 100 °C.

with 3 equiv of Cs_2CO_3 in the microwave reactor furnished **9c** along with its regioisomer **10c** (3.75:1) in 37% overall yield (Scheme 3).

Since the pronucleophiles **1** can be obtained from two aldehydes and the electrophiles **2** can be prepared by condensation of an aldehyde and a nitroalkane, the reported method represents a highly modular synthesis of the pyrrole ring that is amenable to the combinatorial variation of all four substituents.[43] It is distantly related to the Barton−Zard reaction[42] and the Montforts synthesis,[44] which furnish 3,4-disubstituted pyrrole-2-carboxylates. In contrast to the Grob cyclization,[45] the reaction does not involve the formation of N_2O by means of a Nef process.[46,47] While many reported pyrrole syntheses yield only acceptor-substituted products, our protocol also permits the preparation of products devoid of an electron-withdrawing substituent. On the other hand, compounds of this type can be sensitive to aerial oxidation and their longer exposure to halogenated solvents such as $CDCl_3$ should also be avoided to prevent the formation of intensely colored oxidation products.

Experimental Section

The α-(alkylideneamino)nitriles **1a**−**1d**,[32−34] the nitroolefins **2a**−**2d**,[48−51] and the nitroacetate **12**[42] were prepared according to literature procedures. Nitrostilbene **2f** was prepared from a Schiff

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base of benzaldehyde and phenylnitromethane in acetic acid.[52] Phenylnitromethane itself was obtained by reaction of benzyl bromide with silver nitrite in aqueous medium.[53]

(*E*)-4-(2-Nitro-but-1-enyl)benzonitrile (2e).[54] 4-Cyanobenzaldehyde (1.92 g, 14.6 mmol) and ammonium acetate (1.12 g, 14.6 mmol) were heated to reflux in 1-nitropropane (20 mL) overnight. Excess 1-nitropropane was removed in vacuo. The oily residue was dissolved in ethyl acetate (40 mL) and washed with saturated $NaHCO_3$ solution (40 mL), water (40 mL), and brine (40 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo to yield a brown solid (2.71 g). The material was recrystallized from ethanol/petroleum ether to yield **2e** as a slightly ochre solid (0.34 g). A second crop (0.85 g) was obtained from the mother liquor after it stood for 50 h at 4 °C. The remaining mother liquor was concentrated in vacuo and purified by flash chromatography (petroleum ether/ethyl acetate 10:1) to give pure **2e** (0.27 g) as yellow crystals. Combined yield 1.46 g, 50%; mp 109−110 °C; R_f 0.35 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 2230 (s), 1650 (m), 1517 (s), 1502 (m), 1456 (m), 1441 (m), 1326 (s), 1285 (m), 948 (m), 935 (m), 843 (m), 808 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95 (s, 1H, β-CH), 7.73 (AA′ part of AA′BB′ system, 2H, H2,6), 7.48 (BB′ part of AA′BB′ system, 2H, H3,5), 2.80 (q, J = 7.4 Hz, 2H, CH_2), 1.25 (t, J = 7.4 Hz, 3H, CH_3); transient NOE, irradiation at 2.80 ppm (CH_2) enhances the signals at 7.48 (H3,5, 1.0%) and 1.25 (CH_3, 1.5%) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 155.4 (C−NO_2), 137.0 (C4), 132.6 (2C, Ar), 130.6 (β-CH), 129.9 (2C, Ar), 118.0 and 113.3 (C1, CN), 20.7 (CH_2), 12.5 (CH_3) ppm; FD-MS (*m/z*): 202.1 (100%) $[M]^+$. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.33; H, 4.87; N, 13.86.

General Procedure for the Synthesis of Pyrroles (9a−9n): Method A. A mixture of imine **1**, nitroolefin **2** (1−1.5 equiv), and cesium carbonate (2 equiv) in THF (1.8 mL/100 mg of imine) was heated under reflux for several hours under argon atmosphere. After complete conversion (TLC), ethyl acetate and saturated aqueous $NaHCO_3$ solution were added to the reaction mixture. After separation of the organic layer, the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, and filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography or recrystallization.

Method B. A mixture of imine **1**, nitroolefin **2** (1 equiv), and cesium carbonate (2 equiv) in DMF (1 mL/100 mg of imine) was heated to 100 °C in an argon-filled closed vial by irradiation with microwaves for 2 min (CEM Discover, air cooling, IR temperature control, maximum power 100 W). After pressure equilibration, the mixture was quenched with water and extracted with ethyl acetate (3×). The combined organic layers were washed with water (3×) and with brine (1×) and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification of the crude products was carried out as described for method A.

4-(4-Chlorophenyl)-3,5-dimethyl-2-(2-naphthyl)-1*H*-pyrrole (9a) was prepared according to method A from **1a** (500.5 mg, 2.40 mmol), **2a** (474.9 mg, 2.40 mmol), and Cs_2CO_3 (1.56 g, 4.80 mmol) in THF (9 mL). A portion (106.3 mg) of the crude product was recrystallized from methanol to yield **9a** (36.7 mg) as a slightly beige solid. Another portion of **9a** (17.6 mg) was obtained from the mother liquor. Combined yield 54.3 mg, 51% [yield was increased to 54% when **9a** was prepared by microwave heating (method B) from **1a** (99.5 mg, 0.478 mmol), **2a** (94.3 mg, 0.477 mmol), and Cs_2CO_3 (311.5 mg, 0.956 mmol) in DMF (1 mL)]; mp 177−179.5 °C; R_f 0.42 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3447 (s, br), 1628 (m), 1603 (m), 1510 (m), 1490 (s), 1089 (m), 1003 (w), 862 (w), 836 (m), 751 (m) cm^{-1}; ^1H NMR, COSY, HMBC (400 MHz, DMSO-d_6) δ = 11.05 (br s, 1H, NH), 7.92 (mc, 2H, H1′, H4′), 7.88 (mc, 2H, H5′, H8′), 7.70 (dd, J = 8.6, 1.6 Hz, 1H, H3′), 7.52−7.40 (m, 4H, H6′, H7′, H3″,5″), 7.31 (BB′ part of AA′BB′ system, 2H, H2″,6″), 2.25 (s, 3H, 5-CH_3), 2.20 (s, 3H, 3-CH_3) ppm; transient NOE, irradiation at 2.20 ppm (3-CH_3) enhances the signals at 7.92 (H1′, 1.6%), 7.70 (H3′, 1.5%), and 7.31 (H2″,6″, 2.6%) ppm, whereas irradiation at 2.25 ppm (5-CH_3) enhances only the signals at 11.05 (NH, 0.9%) and 7.31 (H2″,6″, 2.9%) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ = 135.2 (C1″), 133.3 (C8a′), 131.2 (C4a′), 131.1 (2C, C2″,6″), 131.0 (C4″), 129.8 (C2′), 128.1 (2C, C3″,5″), 127.8 (C4′), 127.5 (C5′), 127.5 (C8′), 126.3 (C7′), 126.1 (C2), 125.7 (C5), 125.2 and 125.1 (C3′, C6′), 123.3 (C1′), 121.3 (C4), 113.9 (C3), 11.9 (5-CH_3), 11.8 (3-CH_3) ppm. The HMBC spectrum showed correlations between both methyl groups and C4 as well as C1″. Anal. Calcd for $C_{22}H_{18}ClN$: C, 79.63; H, 5.47; N, 4.22. Found: C, 79.62; H, 5.43; N, 4.24. ESI-MS (*m/z*) 331.1 (100) $[M]^+$; ESI-HRMS calcd for $[C_{22}H_{18}ClN + H]^+$ 332.1206, found 332.1216.

3-(4-Chlorophenyl)-4,5-dimethyl-2-(2-naphthyl)-1*H*-pyrrole (10a) and **9a** were obtained as an isomeric mixture prepared according to method A, starting from **1a** (100 mg, 0.48 mmol) and **2a** (94.9 mg, 0.48 mmol) with KO^{t}Bu (146.7 mg, 1.31 mmol) instead of Cs_2CO_3. A portion (85.1 mg) of the crude product (152.2 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to yield a 1.6:1 isomeric mixture of **9a** and **10a** (27.4 mg, 0.083 mmol, 19%) as a slightly yellow foam.

NMR data for **10a** (in $CDCl_3$): ^1H NMR (300 MHz, $CDCl_3$) δ = 8.03 (br s, 1H, NH), 7.75−7.64 (m, 5H, H1′, H3′, H4′, H5′, H8′), 7.54−7.40 (m, 2H, H6′, H7′), 7.30 (AA′ part of AA′BB′ system, 2H, H3″,5″), 7.22 (BB′ part of AA′BB′ system, 2H, H2″,6″), 2.33 (s, 3H, 5-CH_3), 2.03 (s, 3H, 4-CH_3); transient NOE, irradiation at 2.03 ppm (4-CH_3) enhances the signals at 7.30 (H3″,5″, 0.2%), 7.22 (H2″,6″, 1.3%), and 2.33 (5-CH_3, 1.2%) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 135.0 (C1″), 133.6 (C8a′), 131.8 (C4a′), 131.7 (C4″), 131.7 (2C, C2″,6″), 130.7 (C2′), 130.3 (Cq), 128.4 (2C), 128.3, 128.0, 127.6 (2C), 126.2, 125.7, 125.2 (Cq), 124.1 (C1′), 121.7 (Cq), 115.4 (Cq), 11.3 and 9.7 (4-CH_3, 5-CH_3) ppm.

4-(3,4-Dimethoxyphenyl)-3,5-dimethyl-2-(2-naphthyl)-1*H*-pyrrole (9b) was prepared according to method B from **1a** (100.9 mg, 0.484 mmol), **2b** (108.2 mg, 0.485 mmol), and Cs_2CO_3 (314.2 mg, 0.964 mmol) in DMF (1 mL). A portion (206.4 mg) of the crude product (220.0 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to yield **9b** (64.6 mg, 40%) as a slightly pink solid. mp 182−184 °C; R_f 0.15 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3383 (s, br), 1601 (m), 1506 (s), 1463 (m), 1254 (s), 1240 (m), 1136 (m), 1025 (m), 857 (m), 816 (m) cm^{-1}; ^1H NMR, HMBC, COSY (400 MHz, DMSO-d_6) δ = 10.92 (br s, 1H, NH), 7.92−7.90 (m, 2H, H1″, H4″), 7.87 (mc, 2H, H5″, H8″), 7.70 (dd, J = 8.7, 1.6 Hz, 1H, H3″), 7.48 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H, H7″), 7.42 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H, H6″), 6.98 (d, J = 8.2 Hz, 1H, H5′), 6.85 (d, J = 1.8 Hz, 1H, H2′), 6.79 (dd, J = 8.2, 1.8 Hz, 1H, H6′), 3.77 (2s, 2 × 3H, OCH_3), 2.25 (s, 3H, 5-CH_3), 2.21 (s, 3H, 3-CH_3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, DMSO-d_6) δ = 148.8 (C3′), 147.2 (C4′), 133.9 (C8a″), 131.9 (C2″), 131.3 (C4a″), 129.4 (C1′), 128.3 (C4″), 128.0 (2C, C5″, C8″), 126.7 (C7″), 126.1 (C2), 125.7 (C5), 125.5 (C3″), 125.5 (C6″), 123.5 (C1″), 123.1 (C4), 122.1 (C6′), 114.6 (C3), 114.1 (C2′), 112.3 (C5′), 56.0 (OCH_3), 55.9 (OCH_3), 12.5 (3-CH_3), 12.3 (5-CH_3) ppm; ESI-MS (*m/z*) 737.4 (37) $[2M + Na]^+$, 714.4 (30) $[2M]^+$, 713.4 (100) $[2M - H]^+$, 356.2 (18), $[M - H]^+$. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.54; H, 6.44; N, 4.00. ESI-HRMS calcd for $[C_{24}H_{23}NO_2 + H]^+$ 358.1807, found 358.1806.

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3-Ethyl-4,5-dimethyl-2-(2-naphthyl)-1*H*-pyrrole (9c) was prepared according to method B from **1a** (150.0 mg, 0.720 mmol), **2c** (83.0 mg, 0.721 mmol), and Cs_2CO_3 (470.2 mg, 1.44 mmol) in DMF (1 mL). A portion (171.1 mg) of the crude product (181.1 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to yield **9c** (56.6 mg, 0.227 mmol, 33%) as a slightly brown oil. R_f 0.52 (petroleum ether/ethyl acetate 5:1); IR (NaCl, film) ν = 3430 (m), 2960 (s), 2926 (s), 2867 (m), 1628 (m), 1593 (m), 1525 (m), 1461 (m), 854 (m), 820 (m), 749 (s) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.49 (br s, 1H, NH), 7.88−7.80 (m, 4H, H1′, H4′, H5′, H8′), 7.59 (dd, J = 8.6, 1.5 Hz, 1H, H3′), 7.43 (mc, 2H, H6′, H7′), 2.57 (q, J = 7.4 Hz, 2H, CH_2), 2.15 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.14 (t, J = 7.4 Hz, 3H, CH_2CH_3) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ = 133.6 (C8a′), 131.9 (C4a′), 130.9 (C2′), 127.9 (C4′), 127.6 (2C, C5′, C8′), 126.3 (C7′), 125.1 and 125.0 (C3′, C6′), 124.8, 124.4, 122.6 (C1′), 122.1, 113.9 (C4), 18.2 (CH_2), 15.8 (CH_3), 11.0 (CH_3), 9.0 (CH_3) ppm; ESI-HRMS calcd for $[C_{18}H_{19}N + H]^+$ 250.1596, found 250.1591.

4,5-Dimethyl-2-(2-naphthyl)-3-pentyl-1*H*-pyrrole (9d) was prepared according to method B from **1a** (60.9 mg, 0.292 mmol), **2d** (45.9 mg, 0.292 mmol), and Cs_2CO_3 (189.7 mg, 0.582 mmol) in DMF (0.6 mL). A portion (76.4 mg) of the crude product (86.9 mg) was purified by column chromatography (petroleum ether/ethyl acetate 8:1) to yield **9d** (25.5 mg, 0.087 mmol, 34%) as a reddish oil. R_f 0.49 (petroleum ether/ethyl acetate 5:1); IR (NaCl, film) ν = 3430 (br), 2955 (m), 2926 (s), 2857 (m), 1628 (m), 1593 (m), 1466 (m) 890 (w), 855 (m), 748 (m) cm^{-1}; ^{1}H NMR, HMBC, COSY (400 MHz, DMSO-d_6) δ = 10.50 (br s, 1H, NH), 7.87 (d, J = 8.6 Hz, 1H, H4′), 7.83 (d, J = 8.0 Hz, 1H, H5′), 7.81−7.79 (m, 2H, H1′, H8′), 7.60 (dd, J = 8.6, 1.8 Hz, 1H, H3′), 7.46 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H, H7′), 7.40 (ddd, J = 8.0, 6.9, 1.3 Hz, 1H, H6′), 2.54 (mc, 2H, α-CH_2), 2.15 (s, 3H, 5-CH_3), 1.90 (s, 3H, 4-CH_3), 1.51 (mc, 2H, β-CH_2), 1.35−1.30 (m, 4H, γ-,δ-CH_2), 0.85 (mc, 3H, ϵ-CH_3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, DMSO-d_6) δ = 133.9 (C8a′), 132.3 (C2′), 131.2 (C4a′), 128.2 (C4′), 127.9 (C5′), 127.8 (C8′), 126.7 (C7′), 125.4 (C3′), 125.3 (C6′), 125.1 (C5), 124.9 (C2), 122.9 (C1′), 121.2 (C3), 114.5 (C4), 32.0 (γ-C), 30.8 (β-C), 25.4 (α-C), 22.4 (δ-C), 14.5 (ϵ-C), 11.4 (5-CH_3), 9.5 (4-CH_3) ppm; FD-MS m/z = 291.5 (100) $[C_{21}H_{25}N]^+$; ESI-HRMS calcd for $[C_{21}H_{25}N + H]^+$ 292.2065, found 292.2061.

4-(4-Cyanophenyl)-3-ethyl-5-methyl-2-(2-naphthyl)-1*H*-pyrrole (9e) and 3-(4-Cyanophenyl)-4-ethyl-5-methyl-2-(2-naphthyl)-1*H*-pyrrole (10e). Compound **9e** was prepared according to method B, starting from **1a** (150.7 mg, 0.724 mmol), **2e** (146.1 mg, 0.723 mmol), and Cs_2CO_3 (473.4 mg, 1.453 mmol) in DMF (1.5 mL). A portion (106.8 mg) of the crude product (261.8 mg) was purified by column chromatography (petroleum ether/ethyl acetate 8:1) to yield an isomeric mixture of **9e** and **10e** (2.5:1, 23.8 mg, 0.071 mmol, 24%) along with pure **9e** (31.9 mg, 0.095 mmol, 32%) as an orange solid. mp 180−183 °C (decomp); R_f 0.41 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3332 (s), 2226 (s), 1603 (s), 1508 (m), 1496 (m), 844 (m), 748 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.12 (br s, 1H, NH), 7.95−7.83 (m, 6H), 7.67 (dd, J = 8.5, 1.6 Hz, 1H), 7.53−7.73 (m, 4H), 2.71 (q, J = 7.4 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 0.91 (t, J = 7.4 Hz, 3H, CH_2CH_3) ppm; ^{13}C NMR, DEPT (75.5 MHz, DMSO-d_6) δ = 142.3 (Cq), 133.4 (Cq), 132.2 (2C, C2″,6″), 133.1 (Cq), 131.2 (Cq), 130.2 (2C, C3″,5″), 128.0, 127.7, 127.6, 126.7 (Cq), 126.5, 126.3 (Cq), 125.5, 125.5 (overlapping signals), 124.1, 120.8 (Cq), 120.5 (Cq), 119.4 (CN), 107.8 (Cq), 17.8 (CH_2), 15.8, 11.8 (2 × CH_3) ppm; ESI-MS (m/z) 337.1 (28) $[M + H]^+$, 336.1 (100) $[M]^+$, 335.1 (30) $[M - H]^+$; ESI-HRMS calcd for $[C_{24}H_{20}N_2 + H]^+$ 337.1705, found 337.1707. Characteristic ^{1}H NMR shifts of **10e**: ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.10 (br s, 1H, NH), 2.35 (q, J = 7.4 Hz, 2H, CH_2), 2.24 (s, 3H, CH_3), 0.90 (t, J = 7.4 Hz, 3H, CH_3).

5-Methyl-2-(2-naphthyl)-3,4-diphenyl-1*H*-pyrrole (9f) was prepared according to method B, starting from **1a** (99.8 mg, 0.479 mmol), **2f** (108.3 mg, 0.481 mmol), and Cs_2CO_3 (312.9 mg, 0.960 mmol) in DMF (1 mL). A portion (192.3 mg) of the crude product (221.1 mg) was purified by column chromatography (toluene/petroleum ether 2:1) to yield **9f** (50.3 mg, 0.140 mmol, 34%) as a slightly pink foam. R_f 0.47 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3392 (s), 1599 (m), 1499 (m), 864 (m), 825 (m), 772 (m), 759 (m), 739 (s), 700 (s) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.31 (br s, 1H, NH), 7.79−7.77 (m, 2H), 7.68−7.64 (m, 2H), 7.41 (mc, 2H), 7.23−7.16 (m, 6H), 7.12−7.07 (m, 1H), 7.03−7.01 (m, 4H), 2.30 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ = 136.6 (Cq), 136.0 (Cq), 133.2 (Cq), 131.3 (Cq), 130.9 (Cq), 130.7 (2C), 129.9 (2C), 128.1 (2C), 127.8 (2C), 127.6, 127.5, 127.4, 126.3, 126.2 (Cq), 126.1 (Cq), 125.9, 125.7, 125.4, 125.2, 124.2, 121.7 (Cq), 121.3 (Cq), 11.8 (CH_3) ppm; ESI-MS (m/z) 360.2 (32) $[M + H]^+$, 359.2 (100) $[M]^+$, 358.2 (38) $[M - H]^+$; ESI-HRMS calcd for $[C_{27}H_{21}N + H]^+$ 360.1752, found 360.1758.

5-Benzyl-3-(4-chlorophenyl)-4-methyl-2-(2-naphthyl)-4-nitro-3,4-dihydro-2*H*-pyrrole (8g) and 5-benzyl-4-(4-chlorophenyl)-3-methyl-2-(2-naphthyl)-1*H*-pyrrole (9g) were prepared according to method A from **1b** (99.7 mg, 0.351 mmol), **2a** (69.5 mg, 0.352 mmol), and Cs_2CO_3 (231.1 mg, 0.709 mmol) in THF (1.8 mL). A portion (133.0 mg) of the crude product (147.0 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1 + 1% Me_2NEt) to yield **9g** (47.2 mg, 0.116 mmol, 36%) as a slightly beige solid. The side product **8g** was isolated in 31% yield (44.4 mg, 0.098 mmol) as a slightly yellow oil.

Analytical data for **8g**: R_f 0.26 (petroleum ether/ethyl acetate 5:1); IR (NaCl, film) ν = 3060 (w), 1641(w), 1601 (w), 1542 (s), 1494 (m), 1455 (m), 1385 (w), 1347 (w), 1093 (m), 1015 (m), 857 (w), 820 (m), 750 (m), 731 (m), 705 (m) cm^{-1}; ^{1}H NMR, COSY, HMBC (400 MHz, $CDCl_3$) δ = 7.82−7.75 (m, 3H, H4′, H5′, H8′), 7.70 (br s, 1H, H1′), 7.46−7.43 (m, 2H, H6′, H7′), 7.36−7.28 (m, 8H, H3′, H3″,5″, C_6H_5), 7.11−7.09 (m, 2H, H2″,6″), 5.45 (d-pseudo-t, J_d = 9.1 Hz, $J_t \approx$ 1.7 Hz, 1H, H2), 4.32 (d, J = 9.1 Hz, 1H, H3), 4.00 (dd, J = 15.4, 1.3 Hz, 1H, CH_2-H_a), 3.69 (dd, J = 15.4, 2.1 Hz, 1H, CH_2-H_b), 1.22 (s, 3H, CH_3) ppm; transient NOE, irradiation at 1.22 ppm (CH_3) enhances the signals at 7.36 (C_6H_5, 1.2%), 7.11 (H2″,6″, 3.0%), 5.45 (H2, 2.1%), 4.32 (H3, 0.5%), 4.00 (CH_2-H_a, 0.6%), and 3.69 (CH_2-H_b, 1.0%) ppm, whereas irradiation at 4.32 ppm (H3) enhances the signals at 7.70 (H1′, 1.2%), 7.36−7.32 (H3′, 2.1%), 7.11 (H2″,6″, 6.4%), and 5.45 (H2, 1.0%) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ = 172.1 (C5), 137.4 (C2′), 135.1 (C1‴), 134.5 (C4″), 133.2 (C8a′), 133.0 (C4a′), 132.2 (C1″), 130.3 (2C, C2″,6″), 129.3 (2C) and 129.2 (2C), (C3″,5″, C2‴,6‴), 128.8 (2C, C3‴,5‴), 128.7 (C4‴), 128.0 (C8′), 127.7 and 127.3 (C4′, C5′), 126.3 and 126.0 (C6′, C7′), 125.9 (C1′), 124.5 (C3′), 102.6 (C4), 75.6 (C2), 63.7 (C3), 36.7 (CH_2), 17.8 (CH_3) ppm; ESI-HRMS calcd for $[C_{28}H_{23}N_2O_2Cl + Na]^+$ 477.1346, found 477.1364. The compound slowly decomposes in solution.

Analytical data for **9g**: mp 155−157 °C; R_f 0.54 (petroleum ether/ethyl acetate 5:1); IR (NaCl, film) ν = 3420 (br), 1628 (m), 1602 (m), 1488 (s), 1452 (m), 1090 (m), 1003 (m), 832 (s), 820 (m), 748 (m), 728 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92 (br s, 1H, NH), 7.88−7.82 (m, 4H, H1′, H4′, H5′, H8′), 7.58 (dd, J = 8.5, 1.7 Hz, 1H, H3′), 7.50−7.22 (m, 11H), 4.06 (s, 2H, $PhCH_2$), 2.30 (s, 3H, CH_3) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 139.3 (C1‴), 134.5 (Cq), 133.7 (C8a′), 131.9 (Cq), 131.8 (Cq), 131.3 (2C, C2″, 6″), 130.9 (Cq), 128.8 (2C), 128.7 (2C), 128.4 (2C), 128.3, 127.9 (Cq), 127.7 (partly overlapping signals, 3C), 126.6, 126.4, 125.6, 125.1, 124.5, 123.7 (C3), 115.2 (C4), 32.4 (CH_2), 11.5 (CH_3) ppm. Anal. Calcd for $C_{28}H_{22}ClN$: C, 82.44; H, 5.44; N, 3.43. Found: C, 82.60; H, 5.32; N, 3.61. ESI-MS (m/z) 407.3 (45) $[M]^+$, 383.6 (72), 332.1 (90), 320.3 (45), 263.2 (100); ESI-HRMS calcd for $[C_{28}H_{22}ClN + H]^+$ 408.1519, found 408.1511.

5-Benzyl-4-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-3-methyl-1*H*-pyrrole (9h) was prepared according to method A from **1c** (100.3 mg, 0.341 mmol), **2a** (67.2 mg, 0.341 mmol), and Cs_2CO_3 (223.0 mg, 0.684 mmol) in THF (1.8 mL). A portion (128.4 mg) of the crude product (147.4 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1 + 1% Me_2NEt) to yield

9h (52.6 mg, 0.126 mmol, 43%) as a slightly yellow viscous oil. R_f 0.28 (petroleum ether/ethyl acetate 3:1); IR (NaCl, film) ν = 3360 (br), 1601 (m), 1506 (s), 1453 (m), 1249 (s), 1221 (m), 1140 (m), 1090 (m), 1027 (m) 834 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.75 (br s, 1H, NH), 7.40−7.18 (m, 9H), 6.94−6.89 (m, 3H), 4.02 (s, 2H, CH_2Ph), 3.91 (s, 6H, OCH_3), 2.20 (s, 3H, CH_3) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 149.0 (C3′), 147.7 (C4′), 139.4 (Cq), 134.6 (Cq), 131.7 (Cq), 131.2 (2C, C2″, 6″), 128.7 (2C), 128.5 (2C), 128.4 (2C), 127.9 (Cq), 126.7 (Cq), 126.6 (Cq), 126.5, 123.2 (C4), 119.2 (C6′), 113.8 (C3), 111.5 and 110.5 (C2′, C5′), 55.9 (2C, OCH_3), 32.3 (CH_2Ph), 11.2 (CH_3) ppm; ESI-MS (*m/z*) 434.3 (100), 417.3 (40) $[M]^+$, 343.1 (70), 295.2 (54), 263.4 (38); ESI-HRMS calcd for $[C_{26}H_{24}ClNO_2 + H]^+$ 418.1574, found 418.1574.

3-(4-Cyanophenyl)-5-(3,4-dimethoxyphenyl)-4-ethyl-2-phenyl-1*H*-pyrrole (9i) and 3-(4-Cyanophenyl)-2-(3,4-dimethoxyphenyl)-4-ethyl-5-phenyl-1*H*-pyrrole (10i). Compound **9i** was prepared according to method B, starting from **1d** (149.8 mg, 0.534 mmol), **2e** (108.5 mg, 0.537 mmol), and Cs_2CO_3 (356.6 mg, 1.094 mmol) in DMF (1.5 mL). A portion (91.5 mg) of the crude product (195.1 mg) was purified by column chromatography (petroleum ether/ethyl acetate 2:1) to yield an isomeric mixture of **9i** and **10i** (42.5 mg, 0.104 mmol, 42%) as a slightly yellow foam. R_f 0.12 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3426 (s, br), 2226 (m), 1604 (s), 1516 (s), 1496 (s), 1464 (m), 1252 (s), 1225 (m), 1141 (m), 1025 (m), 847 (m), 767 (m), 699 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, ratio of isomers a:b = 3:1) δ = 11.2 (br s, 1H, NH^{a+b}), 7.82−6.70 (m, 12H, Ar^{a+b}), 3.82 (s, 3H, OCH_3^b), 3.78 (s, 3H, OCH_3^b), 3.70 (s, 3H, OCH_3^a), 3.56 (s, 3H, OCH_3^a) 2.53 (q, J = 7.4 Hz, 2H, CH_2^{a+b}), 0.88−0.83 [partly overlapping signals; contains 0.86 (t, J = 7.4 Hz, 3H, CH_3^b), 0.83 (t, J = 7.4 Hz, 3H, CH_3^a] ppm; ^{13}C NMR, DEPT (75.5 MHz, DMSO-d_6, ratio of isomers a:b = 3:1) δ = 149.0 (Cq^b), 148.7 (Cq^a), 147.9 (Cq^a), 148.0 (Cq^b), 143.2 (Cq^a), 143.0 (Cq^b), 133.6 (Cq^a), 132.8 (Cq^b), 132.6 ($2C^{a+b}$), 131.7 ($2C^a$), 131.6 ($2C^b$), 129.8 (Cq^b), 129.7 (Cq^a), 129.0 ($2C^{a+b}$), 128.9 (Cq^{a+b}), 127.9 ($2C^b$), 127.8 ($2C^a$), 126.7^a, 126.6^b, 126.2 (Cq^b), 125.3 (Cq^a), 122.3 (Cq^a), 121.7 (Cq^b), 121.5 (Cq^b), 120.9 (Cq^a), 120.2^a, 120.0^b, 119.6 (CN^{a+b}), 112.3^b, 112.1^a, 112.0^b, 111.8^a, 109.0 (Cq^b), 108.9 (Cq^a), 56.0 (OCH_3^b), 55.9 (OCH_3^b), 55.9 (OCH_3^a), 55.5 (OCH_3^a), 17.8 (CH_2^a), 17.8 (CH_2^b), 16.3 (CH_3^{a+b}) ppm; ESI-MS (*m/z*) 425.1 (83), 409.1 (40) $[M + H]^+$, 408.1 (100) $[M]^+$, 407.1 (60) $[M - H^-]^+$, 282.2 (50); ESI-HRMS calcd for $[C_{27}H_{24}N_2O_2]^+$ 408.1838, found 408.1851.

2-(3,4-Dimethoxyphenyl)-3,4,5-triphenyl-1*H*-pyrrole (9j) was prepared according to method B, starting from **1d** (100.8 mg, 0.357 mmol), **2f** (81.0 mg, 0.360 mmol), and Cs_2CO_3 (233.5 mg, 0.717 mmol) in DMF (1 mL). A portion (161.2 mg) of the crude product (177.4 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to yield **9j** (43.4 mg, 0.101 mmol, 31%) as a slightly yellow solid. mp 198−201 °C; R_f 0.17 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3436 (m, br), 3342 (m), 1602 (m), 1512 (s), 1492 (m), 1461 (m), 1442 (m), 1252 (s), 1224 (m), 1026 (m), 766 (m), 700 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 11.30 (br s, 1H, NH), 7.29−7.24 (m, 4H), 7.17−7.10 (m, 7H), 7.01 (mc, 4H), 6.86−6.83 (m, 3H), 3.70 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ = 148.2 (C3′), 147.4 (C4′), 136.4 (Cq), 136.1 (Cq), 132.8 (Cq), 131.0 (2C), 130.8 (2C), 129.0 (Cq), 128.3 (Cq), 128.2 (2C), 128.1 (4C), 128.0 (2C), 126.2 and 125.9 (2C), 125.3 (Cq), 122.6 (Cq), 122.1 (Cq), 119.7 (C6′), 111.7 and 111.6 (C2′, C5′), 55.5 (OCH_3), 55.0 (OCH_3) ppm; ESI-MS (*m/z*) 448.3 (72), 431.2 (100) $[M]^+$; ESI-HRMS calcd for $[C_{30}H_{25}NO_2]^+$ 431.1885, found 431.1891.

3-Methyl-1-(2-naphthyl)-4,5,6,7-tetrahydro-2*H*-isoindole (9k) was prepared according to method A from **1a** (150.1 mg, 0.721 mmol), **2g** (81.3 μL, 91.6 mg, 0.720 mmol), and Cs_2CO_3 (468.2 mg, 1.437 mmol) in THF (2.6 mL). A portion (153.0 mg) of the crude product (180.0 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1) to yield **9k** (72.9 mg, 0.279 mmol, 46%) as a pink solid. mp 81−83 °C; R_f 0.64 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3446 (m), 3430 (m), 2927 (s), 2846 (m), 1628 (m), 1601 (m), 1525 (m), 854 (m), 823 (m), 749 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.97 (br s, 1H, NH), 7.96−7.70 (m, 4H, H1′, H4′, H5′, H8′), 7.60 (dd, J = 8.6, 1.5 Hz, 1H, H3′), 7.44 (mc, 2H, H6′, H7′), 2.88 (mc, 2H, H_2-7), 2.55 (mc, 2H, H_2-4), 2.26 (s, 3H, CH_3), 1.83 (mc, 4H, H_2-5, H_2-6) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 133.9 (C8a′), 131.3 (2C, C2′, C4a′), 128.2 (C4′), 127.6 and 127.6 (overlapping signals, C5′,-C8′), 126.2 and 124.9 (C6′, C7′), 123.9 (2C, C1′, Cq), 123.4 (Cq), 122.1, 118.7 (Cq), 117.9 (Cq), 24.2 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 21.7 (CH_2), 11.0 (CH_3) ppm; Anal. Calcd for $C_{19}H_{19}N$: C, 87.37; H, 7.33; N, 5.36. Found: C, 87.34; H, 7.23; N, 5.33. ESI-MS (*m/z*) 294.2 (18), 278.2 (40), 261.2 (100) $[M]^+$; ESI-HRMS calcd for $[C_{19}H_{19}N + H]^+$ 262.1596, found 262.1586.

3-Benzyl-1-(2-naphthyl)-4,5,6,7-tetrahydro-2*H*-isoindole (9l) and 4-Amino-3-benzyl-1-(2-naphthyl)-5,6,7,8-tetrahydroisoquinoline (11). Compound **9l** was prepared according to method A from **1b** (150.6 mg, 0.530 mmol), **2g** (59.5 μL, 67.1 mg, 0.528 mmol), and Cs_2CO_3 (343.6 mg, 1.055 mmol) in THF (2.6 mL). A portion (162.9 mg) of the crude product (178.5 mg) was purified by column chromatography (petroleum ether/ethyl acetate 5:1 + 1% *i*-$PrNH_2$) to yield **9l** (59.7 mg, 0.177 mmol, 37%) as a pink solid. Side product **11** was isolated in 17% yield (29.1 mg) as a slightly yellow oil.

Analytical data for **9l:** mp 106−107.5 °C; R_f 0.51 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3426 (s), 2926 (m), 2914 (m), 1626 (m), 1586 (w), 1510 (m), 1493 (w), 846 (m), 829 (m), 745 (m), 733 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.84 (br s, 1H, NH), 7.79 (mc, 3H, H4′, H5′, H8′), 7.72 (s, 1H, H1′), 7.48−7.24 (m, 8H, H3′, H6′, H7′, C_6H_5), 3.99 (s, 2H, $PhCH_2$), 2.90, 2.60 (2 mc, 2 × 2H, H_2-4, H_2-7), 1.84 (mc, 4H, (H_2-5, H_2-6) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 139.4 (C1″), 133.8 (C8a′), 131.3 (C2′), 131.2 (C4a′), 128.7 (2C), 128.6 (2C), 128.2, 127.6, and 127.6 (partly overlapping signals), 126.4, 126.2, 126.0 (Cq), 125.0, 124.7 (Cq), 123.9, 122.3, 118.7 (Cq), 118.6 (Cq), 32.2 ($PhCH_2$), 24.2 (CH_2), 24.0 (CH_2), 23.6 (CH_2), 21.7 (CH_2) ppm. Anal. Calcd for $C_{25}H_{23}N$: C, 88.98; H, 6.87; N, 4.15. Found: C, 88.82; H, 6.78; N, 4.08. ESI-MS (*m/z*) 370.3 (35), 354.3 (30), 337.2 (100) $[M]^+$, 262.1 (100); ESI-HRMS calcd for $[C_{25}H_{23}N + H]^+$ 338.1909, found 338.1921.

Analytical data for **11:** R_f 0.14 (petroleum ether/ethyl acetate 5:1); IR (NaCl, film) ν = 3386 (w), 3057 (w), 2932 (m), 2858 (m), 1620 (m), 1605 (m), 1494 (m), 1440 (m), 1424 (s), 1330 (w), 1266 (w), 897 (m), 821 (m), 736 (s), 704 (m) cm^{-1}; ^1H NMR, COSY, HMBC (400 MHz, $CDCl_3$) δ = 7.96 (br d, J = 1.7 Hz, 1H, H1′), 7.91−7.86 (m, 3H, H4′, H5′, H8′), 7.67 (dd, J = 8.4, 1.7 Hz, 1H, H3′), 7.51−7.47 (m, 2H, H6′, H7′), 7.33−7.31 (m, 4H, H2″,6″, H3″,5″), 7.25−7.21 (m, 1H, H4″), 4.25 (s, 2H, $PhCH_2$), 3.51 (br s, 2H, NH_2), 2.73 (t, J = 6.2 Hz, 2H, H_2-8), 2.49 (t, J = 6.6 Hz, 2H, H_2-5), 1.89 (mc, 2H, H_2-6), 1.69 (mc, 2H, H_2-7) ppm; ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ = 148.2 (C1), 141.5 (C3), 138.7 (2C, C2′, C1″), 137.7 (C4), 133.3 (C8a′), 132.6 (C4a′), 130.4 (C4a), 129.6 (C8a), 128.7 (2C, C2″,6″), 128.5 (2C, C3″,5″), 128.2 (2C, C1′, Naph-CH), 127.8 (Naph-CH), 127.6 (C3′), 127.5 (Naph-CH), 126.5 (C4″), 125.9 and 125.8 (C6′, C7′), 41.4 ($PhCH_2$), 28.2 (C8), 24.2 (C5), 22.5 (C7), 22.2 (C6) ppm; ESI-HRMS calcd for $[C_{26}H_{24}N_2 + H]^+$ 365.2018, found 365.2027.

3-Benzyl-1-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydro-2*H*-isoindole (9m) was prepared according to method A from **1c** (150.0 mg, 0.510 mmol), **2g** (86.2 μL, 97.2 mg, 0.764 mmol, 1.5 equiv), and Cs_2CO_3 (331.0 mg, 1.019 mmol) in THF (2.6 mL). After the mixture was refluxed for 2 h, another portion of **2g** (57.5 μL, 64.8 mg, 0.510 mmol) was added. After 3 h, the same amount of **2g** was added and the reaction mixture was stirred overnight at 60 °C. A portion (250.2 mg) of the crude product (263.6 mg) was purified by column chromatography (CH_2Cl_2/petroleum ether/ethyl acetate 3:3:0.1) to yield **9m** (63.5 mg, 38%) as a yellow solid. The yield was increased to 51% when **9m** was prepared according to the general procedure (method B) from **1c** (100.3 mg, 0.341 mmol), **2g** (39.1 μL, 44.1 mg, 0.347 mmol), and Cs_2CO_3 (223.2 mg, 0.685

mmol) in DMF (1 mL). The crude product was purified by column chromatography with petroleum ether and ethyl acetate (3:1). mp 119−123 °C; R_f 0.18 (petroleum ether/ethyl acetate 5:1), R_f 0.23 (petroleum ether/CH_2Cl_2/ethyl acetate 3:3:0.1); IR (KBr) ν = 3386 (s), 2939 (m), 2915 (m), 1528 (s), 1261 (m), 1219 (m), 1144 (m), 1023 (m), 737 (w), 700 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 10.52 (br s, 1H, NH), 7.29−7.14 (m, 5H, C_6H_5), 7.03 (s, 1H, H2′), 6.93 (mc, 2H, H5′, H6′), 3.83 (s, 2H, $PhCH_2$), 3.78 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.63 (mc, 2H, H_2-7), 2.37 (mc, 2H, H_2-4), 1.64 (mc, 4H, H_2-5, H_2-6) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ = 148.9 (C3′), 146.2 (C4′), 140.8 (C1″), 128.4 (2C, C_6H_5), 128.3 (2C, C_6H_5), 127.4 (Cq), 125.8, 125.1 (Cq), 123.6 (Cq), 116.8, 116.6 (Cq), 115.9 (Cq), 112.4, 108.9, 55.7 (OCH_3), 55.6 (OCH_3), 31.6 ($PhCH_2$), 24.1 (CH_2), 23.9 (CH_2), 23.4 (CH_2), 21.6 (CH_2) ppm; ESI-MS (*m/z*) 380.3 (20), 364.3 (33), 347.3 (100) $[M]^+$, 272.1 (46); ESI-HRMS calcd for $[C_{23}H_{25}NO_2 + H]^+$ 348.1964, found 348.1960.

1-(3,4-Dimethoxyphenyl)-3-phenyl-4,5,6,7-tetrahydro-2*H*-isoindole (9n) was prepared according to method A from **1d** (150.4 mg, 0.537 mmol), **2g** (66.4 μL, 64.6 mg, 0.589 mmol), and Cs_2CO_3 (349.3 mg, 1.072 mmol) in THF (2.6 mL). A portion (183.4 mg) of the crude product (193.8 mg) was purified by column chromatography (CH_2Cl_2/petroleum ether/ethyl acetate 3:3:0.1) to yield **9n** (56.0 mg, 0.168 mmol, 33%) as a slightly beige foam. The yield was increased to 43% when **9n** was prepared according to method B from **1d** (119.5 mg, 0.426 mmol), **2g** (53.1 μL, 59.9 mg, 0.471 mmol), and Cs_2CO_3 (281.2 mg, 0.863 mmol) in DMF (1.2 mL). The crude product was purified by column chromatography (petroleum ether/ethyl acetate 5:1). R_f 0.20 (petroleum ether/ethyl acetate 5:1); IR (KBr) ν = 3371 (m), 2929 (m), 1603 (m), 1528 (m), 1504 (s), 1463 (m), 1440 (m), 1252 (s), 1224 (m), 1142 (m), 1025 (m), 766 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 10.70 (br s, 1H, NH), 7.54 (d, J = 7.7 Hz, 2H, H2″,6″), 7.38 (t, J = 7.7 Hz, 2H, H3″,5″), 7.18−7.13 (m, 2H, H4″, H2′), 7.07 (dd, J = 8.4, 1.5 Hz, 1H, H6′), 6.97 (d, J = 8.4 Hz, 1H, H5′), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.69 (mc, 4H, H_2-4, H_2-7), 1.71 (mc, 4H, H_2-5, H_2-6) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ = 148.8 (C3′), 146.9 (C4′), 133.6 (Cq), 128.5 (2C), 126.9 (Cq), 126.6 (Cq), 125.8 (Cq), 125.6 (2C), 125.0, 118.5 (Cq), 118.1, 117.5 (Cq), 112.1, 110.0, 55.7 (2C, OCH_3), 23.9, 23.8, 23.7, 23.7 (partly overlapping signals, CH_2) ppm; ESI-MS (*m/z*) 350.3 (100), 333.2 (70) $[M]^+$, 212.1 (49); ESI-HRMS calcd for $[C_{22}H_{23}NO_2 + H]^+$ 334.1807, found 334.1811.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft. We thank H. Kolshorn for the NMR spectroscopic analyses.

Supporting Information Available: ^1H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070426X