One-Pot Synthesis of Pyrrolo[3,2-*f*]- and Pyrrolo[2,3-*h*]quinoline Derivatives: Observation of an Unexpected Mechanistic Pathway

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Abstract: One-pot synthesis of pyrrolo[3,2-*f*]- and pyrrolo[2,3-*h*]quinolines were obtained starting from substituted 5-aminoindoles, benzaldehydes, and phenylacetylenes in the presence of $La(OTf)_3$ as a catalyst in good yields. The indole moiety in 5-aminoindole is believed to be mainly responsible for the observation of unexpected mechanistic pathway to the formation of pyrrolo[2,3-*h*]quinoline.

Key words: pyrroloquinoline, one-pot synthesis, 5-aminoindole, Lewis acid

Nitrogen-containing heterocycles are playing an important role as synthetic building blocks.[1] Recently, great interest has arisen in the synthesis of compounds containing a quinoline or indole moiety.[2] Pyrroloquinolines are nitrogen-containing heterocyclic compounds having fused structures of pyrrole and quinoline.

These important heterocyclic compounds are commonly found in natural products and biologically active compounds such as (±)-martinellic acid,[3a] ammosamides,[3b] batzelline D,[3c] mycenarubins,[3d,e] arnoamine A,[3f] and isobatzellines.[3g] These polycyclic heterocyclic compounds exhibit pharmacological effects due to their angular aromatic tricyclic or tetracyclic system which are suitable for

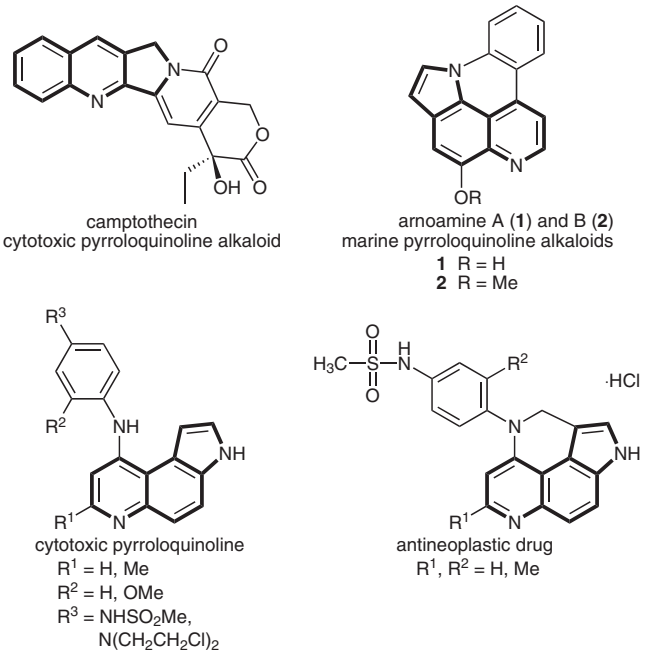

Figure 1 Selected examples of biologically active pyrroloquinolines

Table 1 Optimization of the Reaction Conditions[a]

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	–	MeCN	48	–
2	$La(OTf)_3$	MeCN	3	35/18
3	$PdCl_2$	MeCN	24	–
4	$Pd(OAc)_2$	MeCN	24	–
5	CuI	MeCN	24	–
6	AgOTf	MeCN	24	–
7	Ag_2CO_3	MeCN	24	–
8	$InCl_3$	MeCN	20	20/7
9	$In(OTf)_3$	MeCN	22	15/8
10	$Cu(OTf)_2$	MeCN	24	–
11	TEMPO	MeCN	24	–
12	AIBN	MeCN	24	–
13	$La(OTf)_3$	EtOH	10	28/17
14	$La(OTf)_3$	THF	15	32/15
15	$La(OTf)_3$	CH_2Cl_2	10	29/10
16	$La(OTf)_3$	[Bmim][Cl]	4	44/22
17	$La(OTf)_3$	[Bmim][BF_4]	3	46/27
18	$La(OTf)_3$	[Bmim][PF_6]	3	43/20
19	$La(OTf)_3$	DMF	8	44/20
20	$La(OTf)_3$	DMSO	10	33/19
21[c]	$La(OTf)_3$	[Bmim][BF_4]	5	46/27

[a] General conditions: aminoindole **1a** (1.0 mmol), aldehyde **2a** (1.0 mmol), and acetylene **3a** (1.0 mmol).
[b] Yield refers to column purified product. For the entries 1–12 reflux temperature of MeCN was maintained. For the entries 13–15, and 19 reflux temperature of the corresponding solvents were maintained. Temperature was maintained 90–95 °C for all the ionic liquids (entries 16–18, and 21, 1.0 mL). In all entries, catalyst 10 mol% was calculated relative to the aminoindole **1a**.
[c] For entry 21, catalyst 20 mol% was calculated.

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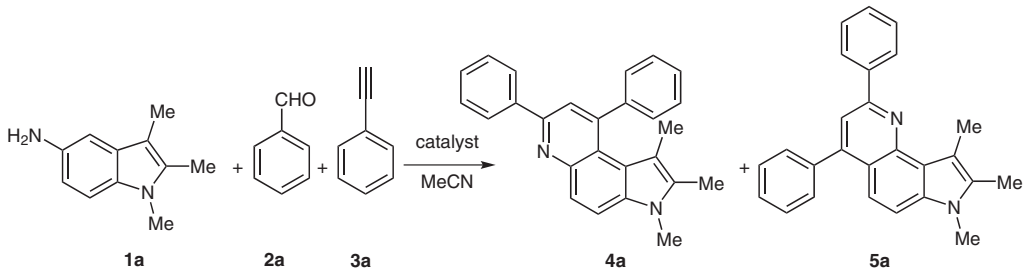


Scheme 1 Synthesis of pyrroloquinolines **4a** and **5a**

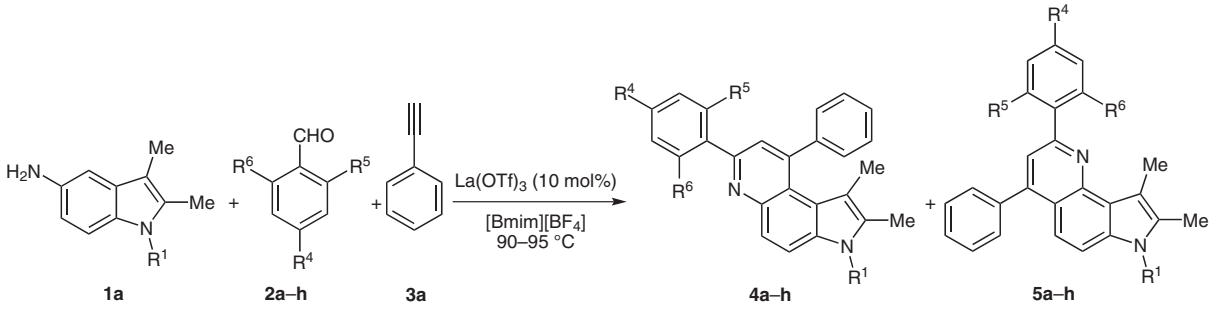
binding with biological targets.[3h] Particularly, we are focusing on pyrrolo[3,2-*f*]- and pyrrolo[2,3-*h*]quinoline derivatives. These pyrroloquinoles (Figure 1) have a wide range of biological applications including antitopoisomerase-II,[4a] antiproliferative[4a] antineoplastic,[4b] cytotoxic,[4c] antimitotic,[4d] and vasco-relaxing[4e] activities. Developing a new methodology to synthesize pyrroloquinolines in a simple one-pot fashion is desirable because most methods of synthesizing these pyrroloquinoline derivatives require several steps and give products in poor yields.[5] Despite several other methods to synthesize these compounds,[6] the synthesis of these types of pyrroloquinolines from aminoindoles in a one-pot approach using typical Lewis acid is unknown at present.

Initially, our studies were commenced with the reaction of 1,2,3-trimethyl-1*H*-5-indolamine (**1a**), benzaldehyde (**2a**), and phenylacetylene (**3a**) as the model substrates to optimize the reaction conditions at reflux temperature of MeCN (Scheme 1). In the absence of catalyst, no desired product was observed (Table 1, entry 1). However, switching to $La(OTf)_3$ as the catalyst resulted in 1,2,3-trimethyl-7,9-diphenyl-3*H*-pyrrolo[3,2-*f*]quinoline (**4a**) and 7,8,9-trimethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (**5a**) in 53% overall yield (Table 1, entry 2). Typical soft metal salts, such as $PdCl_2$, $Pd(OAc)_2$, AgOTf, Ag_2CO_3, CuI, and $Cu(OTf)_2$ were ineffective for the synthesis of these compounds (Table 1, entries 3–7, and 10). Interestingly, the use of indium salts, such as $InCl_3$ and $In(OTf)_3$ moderately enhanced the yields of the products (Table 1, entries 8 and 9). Radical generators such as TEMPO and AIBN could not be able to afford the desired products (Table 1, entries 11 and 12). On the other hand, the use of various solvents such as EtOH, CH_2Cl_2, THF, DMF, and DMSO led to the formation of **4a** and **5a** in lower yields (Table 1, entries 13–15, 19, and 20). In toluene or under neat conditions, no reaction was observed. Ionic liquids such as [Bmim][Cl], [Bmim][BF_4], and [Bmim][PF_6] were also tested (Table 1, entries 16–18, 21); the best result was obtained when [Bmim][BF_4] was used as solvent (Table 1, entry 17). The yield of the reaction could not be increased by raising the catalytic amount of $La(OTf)_3$ from 10 mol% to 20 mol% (Table 1, entry 21).

When lower or higher temperatures were chosen, the product yields decreased; so that at 90–95 °C an optimum was determined.

The scope of the reaction was investigated with various aromatic aldehydes (**2a–h**), 5-aminoindoles (**1a–i**),[8] and phenylacetylenes (**3a–e**) under the optimized reaction conditions (Table 1, entry 17). For benzaldehydes (**2a–h**), the presence of electron-donating groups (Me, OMe, 2,4,6-trimethyl, Table 2, entries 5–7) and electron-withdrawing groups (F, Cl, Br, Table 2, entries 2–4, and 8) did not show significant effects on the yield of the products. However, substitution pattern on first, second, and third positions in 5-aminoindole significantly changed the reaction yield (Table 3, Scheme 3). As expected, different 1-alkyl and benzyl 2, 3-dimethyl-5-aminoindoles were tolerated by the reaction under the optimized conditions.

However, the electron-withdrawing group -SO_2Ph was not suitable in this reaction. No desired products were observed when 5-aminoindoles (**1f–i**) were employed in the reaction with **2a** and **3a** (Table 3, entry 6). We reasoned that the absence of a methyl group at the third position of 5-aminoindoles (**1f–i**) might not facilitate the possible delocalization as shown in Scheme 2. Under the optimized conditions, the scope of this reaction was examined with different acetylenes (**3a–f**). Results are shown in Table 4



Scheme 2 Reaction with different aromatic aldehydes **2a–h**

Table 2 Reaction with Different Aromatic Aldehydes **2a–h**

Entry[a]	Aldehydes	Time (h)	Products	Yield (%)
1	**2a** R^4 = H	3	**4a/5a** R^4 = H	46/27
2	**2b** R^4 = F	3	**4b/5b** R^4 = F	50/25
3	**2c** R^4 = Cl	3	**4c/5c** R^4 = Cl	47/25
4	**2d** R^4 = Br	3.5	**4d/5d** R^4 = Br	49/23
5	**2e** R^4 = Me	4	**4e/5e** R^4 = Me	46/28
6	**2f** R^4 = MeO	3	**4f/5f** R^4 = MeO	48/25
7	**2g** R^4, R^5, R^6 = Me	4	**4g/5g** R^1, R^4, R^5, R^6 = Me	46/24
8	**2h** R^4, R^6 = H, R^5 = Cl	4	**4h/5h** R^1, R^4, R^6 = H, R^5 = Cl	42/23

[a] For entries 1–6, R^1 = Me, R^5, R^6 = H.

Table 3 Reaction with Different 5-Aminoindoles **1a–i**

Entry[a]	Aminoindoles	Time (h)	Products	Yield (%)
1	**1a** R^1, R^2, R^3 = Me	3	**4a/5a**	46/27
2	**1b** R^2, R^3 = Me, R^1 = Et	3	**4i/5i**	50/26
3	**1c** R^2, R^3 = Me, R^1 = Bn	3.5	**4j/5j**	46/24
4	**1d** R^1 = H, R^2, R^3 = Me	4.5	**4k/5k**	42/22
5	**1e** R^1 = H, R^7 = Cl, R^2, R^3 = Me	4	**4l/5l**	45/27
6	**1f** R^1 = SO_2Ph, R^2, R^3 = Me **1g** R^1, R^3 = H, R^2 = Me **1h** R^1, R^2, R^3 = H **1i** R^1, R^2 = Me, R^3 = H	24	–	–

[a] For entry 1-4 and 6, R^7 = H.

and Scheme 4. Satisfactory yields were obtained from phenylacetylenes bearing electron-donating groups [4-OMe (**3b**), 4-Me (**3c**), Table 4, entries 2 and 3]. But the reaction with *O*-nitrophenylacetylene (**3d**), diphenylacetylene (**3e**), and 1-octyne (**3f**) (Table 4, entry 4) did not afford the corresponding pyrroloquinoline derivatives. The structure of the products **4a** and **5g** was ascertained by single-crystal X-ray analysis (Figure 2 and Figure 3).[7]

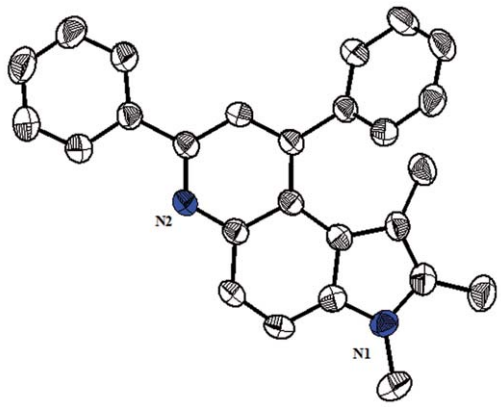


Figure 2 ORTEP diagram of compound **4a**

Table 4 Reaction with Different Acetylenes **3a–f**

Entry[a]	Acetylenes	Time (h)	Products	Yield (%)
1	**3a** R^5 = H	3	**4a/5a**	46/27
2	**3b** R^5 = MeO	3	**4m/5m**	50/26
3	**3c** R^5 = Me	3	**4n/5n**	52/27
4	**3d**,**e**,**f**	24	–	–

[a] For entries 1 and 2, R^1 = Me; for entries 3 and 4, R^1 = H.

According to the above experimental results, a possible reaction mechanism that accounts for the formation of **4a** and **5a** is shown in Scheme 5. Thus condensation of 5-aminoindole **1a** with benzaldehyde (**2a**) gives the imine **A**. Then [4+2] cycloaddition between phenylacetylene (**3a**) and azadiene **A** provides **4a** as major product (path A). Since other amines (3-aminocarbazole, aniline, and 2-naphthylamine) did not afford the unexpected product like

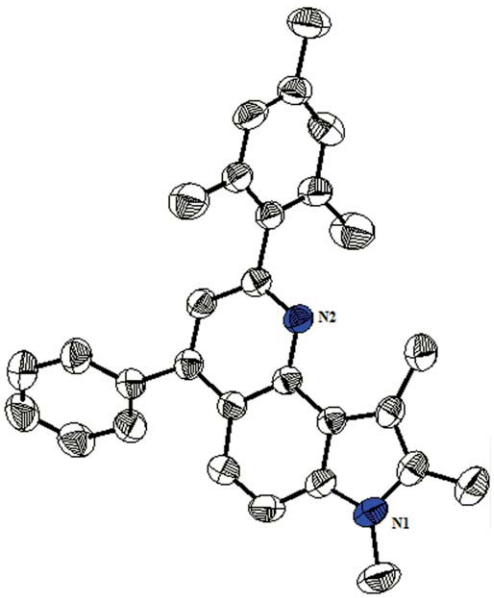
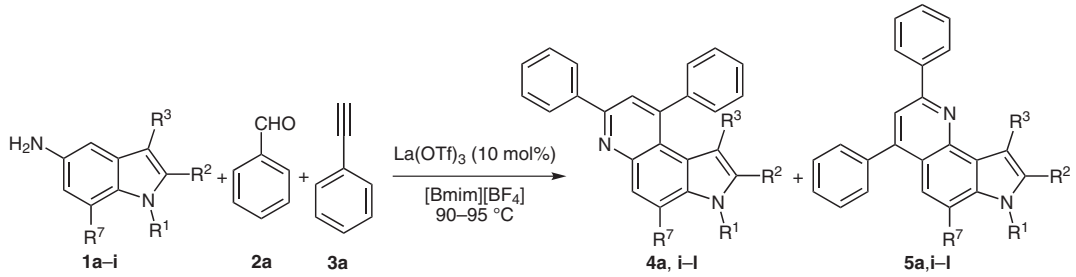


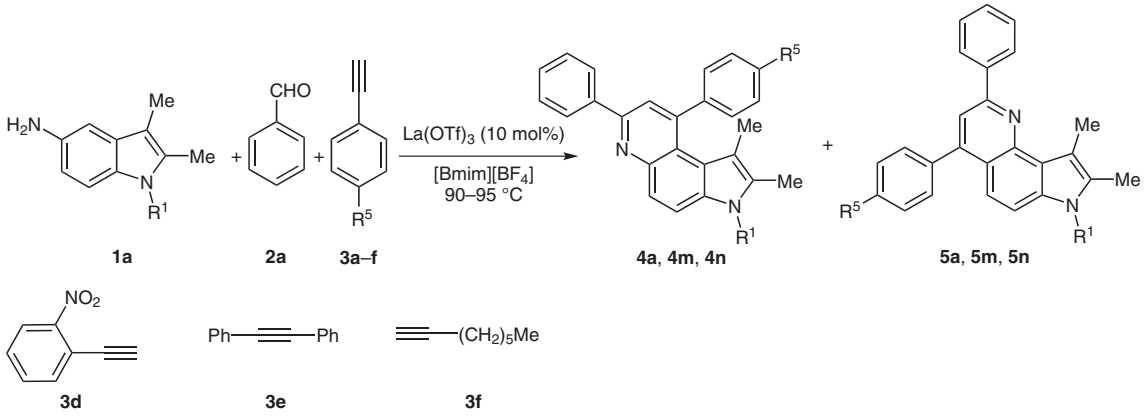
Figure 3 ORTEP diagram of compound **5g**

5a under Lewis acid catalysis,[9] we assume that the presence of the indole moiety in intermediate **A** would be a key role for [3+2] cycloaddition which affords the unexpected product **5a**. The formation of **5a** can be considered as a result of the five-membered intermediate **C**[10] in path B as depicted in Scheme 5.

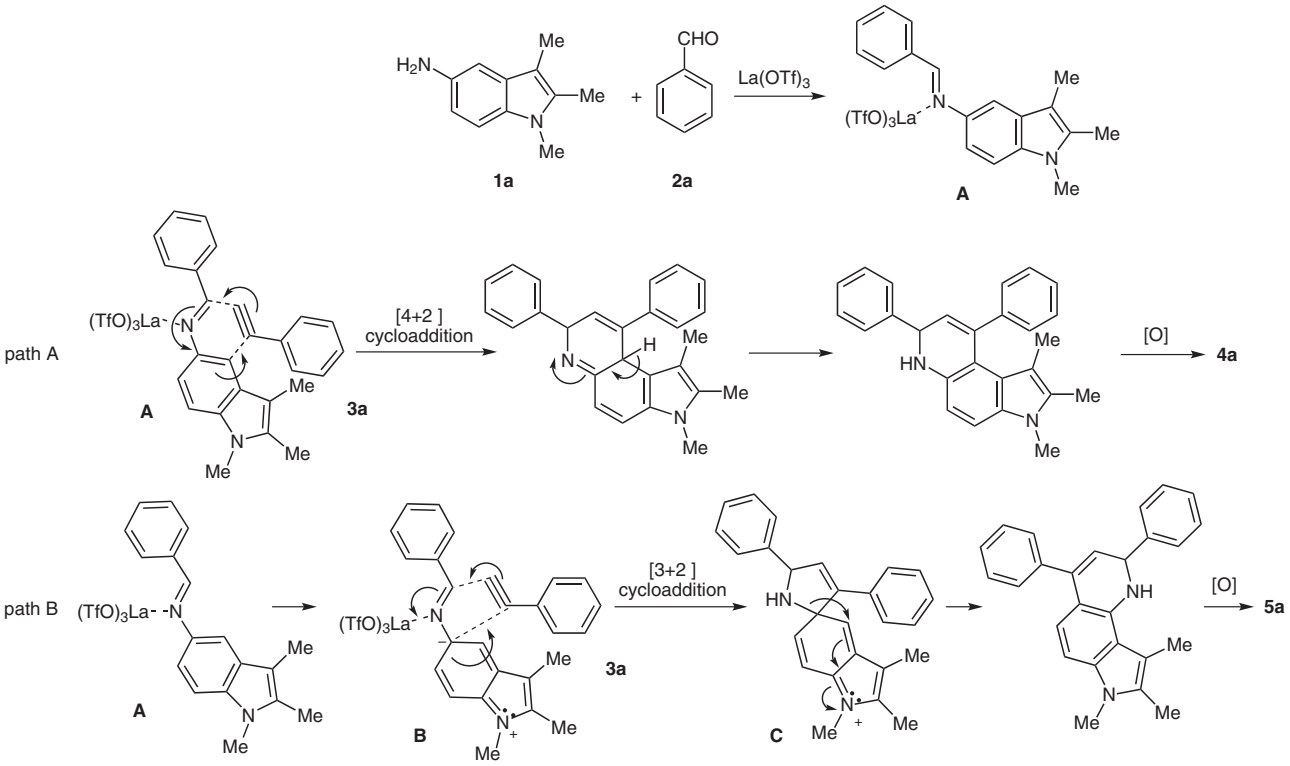
In summary, we have developed an efficient, simple, and high-yielding method for the preparation of pyrrolo[3,2-



Scheme 3 Reaction with different 5-aminoindoles **1a–i**



Scheme 4 Reaction with different acetylenes **3a–f**



Scheme 5 Proposed mechanism for the synthesis of **4a** and **5a**

f]quinoline and pyrrolo[2,3-*h*]quinoline derivatives exploiting a one-pot process using easily accessible starting materials such as indoloamines, benzaldehydes, and phenylacetylenes. To our best knowledge, this is the first report to make these two pyrroloquinolines in one step. We have also observed an interesting and unexpected mechanistic pathway in this reaction.

A Typical Procedure for the Preparation of 4a and 5a

In a round-bottom flask equipped with a magnetic stirring bar, to a mixture of 1,2,3-trimethyl-1*H*-indol-5-ylamine (**1a**, 1.0 mmol), benzaldehyde (**2a**, 1.0 mmol), and phenylacetylene (**3a**, 1.0 mmol) in ionic liquid [Bmim][BF_4] (5 mL) as solvent was added of La(OTf)$_3$ (10 mol%). The reaction mixture was stirred at 90–95 °C for 4 h. After completion of the reaction as indicated by the TLC, H_2O (20 mL) was added to the crude reaction mass. Then aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under the reduced pressure. The product was purified by column chromatography on silica gel (eluent: hexanes–EtOAc). Compounds **4a** and **5a** were afforded in 46% and 27% yield, respectively. R_f (**4a**) = 0.36 and R_f (**5a**) = 0.78 (10% of EtOAc in hexanes).

1,2,3-Trimethyl-7,9-diphenyl-3*H*-pyrrolo[3,2-*f*] Quinoline (4a)

Mp 138–140 °C. IR (KBr): 3055, 1556, 1026, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.20 (2 H, d, *J* = 8.0 Hz), 7.94 (1 H, d, *J* = 8.0 Hz), 7.72 (1 H, s), 7.67 (1 H, d, *J* = 8.0 Hz), 7.52–7.54 (2 H, m), 7.46–7.50 (2 H, m), 7.38 (4 H, m), 3.60 (3 H, s), 2.19 (3 H, s), 1.20 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 152.7, 147.4, 147.1, 144.2, 139.9, 134.1, 132.8, 130.1, 129.3, 128.8, 128.3, 127.6, 127.4, 121.0, 120.7, 120.0, 114.5, 111.2 (arom. C); 30.1, 12.0, 10.5 (aliph. C). MS (positive mode): *m/z* = 363 [M + H]. Anal. Calcd (%) for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.21; H, 6.18; N, 7.65.

7,8,9-Trimethyl-2,4-diphenyl-7*H*-pyrrolo[2,3-*h*]quinoline (5a)

Mp 200–202 °C. IR (KBr): 3042, 1558, 767, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.38 (2 H, d, *J* = 7.6 Hz), 7.78 (1 H, s), 7.59–7.61 (3 H, m), 7.50–7.56 (5 H, m), 7.40–7.46 (2 H, m), 3.78 (3 H, s), 2.9 (3 H, s), 2.48 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 153.8, 148.9, 145.7, 140.5, 140.3, 135.2, 131.8, 129.8, 128.8, 128.7, 128.4, 127.9, 127.3, 122.4, 120.9, 117.8, 115.5, 111.2, 111.1 (arom. C); 29.4, 12.4, 10.1 (aliph. C). MS (positive mode): *m/z* = 363 [M + H]. Anal. Calcd (%) for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.05; H, 6.18; N, 7.68.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) The CCDC deposition number for compound **4a** is 796984. Formula: $C_{26}H_{22}N_2$. Unit cell parameters: a = 7.3436 (16), b = 11.1808 (17), c = 12.467 (3), α = 99.382 (15), β = 102.495 (19), γ = 94.742 (15), space group P-1. The CCDC deposition number for compound **5g** is 796985. Formula: $C_{58}H_{56}N_4$. Unit cell parameters: a = 8.3864 (9), b = 13.2389 (14), c = 21.6848 (19), α = 80.350 (8), β = 82.567 (8), γ = 82.391 (9), space group P-1.

(8) See the Supplementary Information for 5-aminoindoles **1a**–**h** preparation.

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