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Synthesis of Structurally Diverse Polyfunctional Pyrrolo[1,2-*a*]quinolines by Sequential Iron-Catalyzed Three-Component Coupling and Gold-Catalyzed Hydroarylation Reactions

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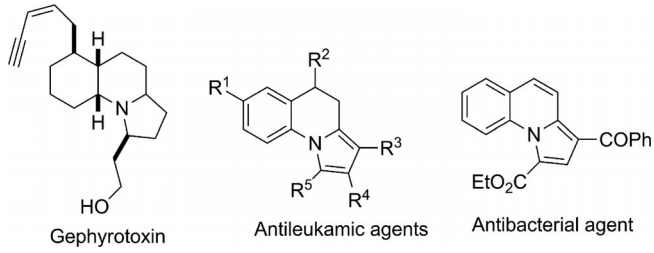
A simple and efficient synthesis of complex pyrrolo[1,2-*a*]-quinoline derivatives was achieved through sequential reactions that involved an iron(III)-catalyzed synthesis of *N*-(2-alkynylaryl)pyrroles and a gold(III)-catalyzed intramolecular hydroarylation reaction. This strategy tolerated a wide range of substrates with a variety of sensitive functional groups and afforded the corresponding pyrrolo[1,2-*a*]quinoline derivatives in moderate to good yields. The ease of availability of the starting materials and the generality of the reaction sequences make it a highly attractive strategy to synthesize a diverse range of pyrrolo[1,2-*a*]quinoline derivatives. Moreover, a preliminary photophysical study showed that the resulting molecules exhibit good fluorescence activity.

Introduction

Fused nitrogen heterocycles are very important because of their occurrence in numerous natural products and their significant role in the pharmaceutical industry and materials science.[1] Among the various fused nitrogen heterocycles, substituted pyrrolo[1,2-*a*]quinolines and their oxidized and reduced forms are widespread among natural products and biologically active pharmaceuticals.[2] Pyrrolo[1,2-*a*]-quinoline skeletons are present in many biologically active natural alkaloids such as gephyrotoxin (see Scheme 1), which is a substituted perhydropyrrolo[1,2-*a*]quinoline that was isolated by Daly and co-workers in 1977 from secretions of the frog *Dendrobates histrionics*.[3] Gephyrotoxin was studied for its biological activity and has been a target for total synthesis.[4] These compounds can act as muscarinic antagonists and exhibit an array of neurological activities.[5] In addition, derivatives of pyrrolo[1,2-*a*]quinoline are known to have antitumor,[6] antibacterial,[7] and antifungal[8] activities (see Scheme 1). These tricyclic ring compounds also possess interesting electron-transport properties.[9] Because of their potential biological activity and attractive physicochemical properties, considerable attention has been paid to the synthesis of functionalized pyrrolo[1,2-*a*]quinolines.



Scheme 1. A few examples of pyrrolo[1,2-*a*]quinoline-containing natural products and pharmaceuticals.

The most common approach to the synthesis of this class of molecules involves a [3+2] cycloaddition of heterocyclic *N*-ylides with electron-deficient alkynes or alkenes[10] and their multicomponent[11] version. Very recently, a few new methods such as intra- and intermolecular alkenylation reactions,[12] a multicomponent coupling reaction,[13] a gold(I)-catalyzed tandem cyclization of 1,4-aminoalkynes with alkynes,[14] rearrangement reactions,[15] as well as a few others[16] have also been developed. Despite these advances, many of these protocols have some limitations such as harsh reaction conditions, low chemical yields, unavailability of starting materials, or unsatisfactory scope and efficiency. Therefore, the development of efficient methodologies to prepare functionally diverse pyrrolo[1,2-*a*]quinoline molecules in a few steps by using readily available starting materials under mild conditions is still highly desirable.

In this regard, multicomponent reactions (MCRs) have received increased attention because of their simplicity, efficiency, atom economy, and their potential for diversity-oriented synthesis.[17] Moreover, such reactions are economically and environmentally attractive and have become an

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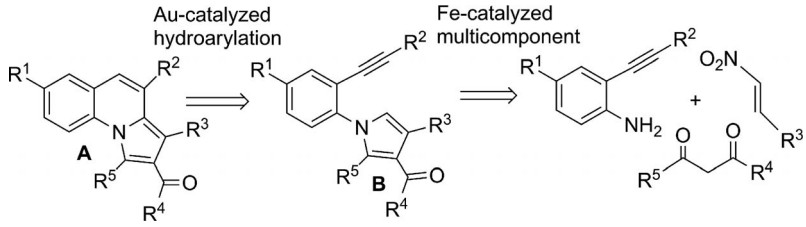


Scheme 2. Retrosynthetic analysis of pyrrolo[1,2-*a*]quinolines.

important area of research in organic chemistry. Therefore, the synthesis of functional molecules by using MCRs is presently a subject of interest. However, the metal-catalyzed intramolecular hydroarylation of alkynes with aromatic rings has recently proved to be a valuable synthetic method to construct useful carbo- and heterocycles.[18,19] This strategy is highly atom-efficient by nature, and, hence, environmentally friendly as no byproducts are formed. Therefore, the synthesis of complex heterocycles by using the multicomponent coupling approach and subsequent intramolecular hydroarylation of the suitably tethered alkyne unit would be highly attractive. This strategy would provide rapid access to a diverse library of heterocyclic molecules that are useful for their biological activities and for photophysical studies.

During the course of our recent studies to develop new and efficient iron-catalyzed methods for the synthesis of useful molecules such as pyrroles, 2*H*-chromenes, phenanthrenes, fluorenes, and other molecules,[20] we envisioned that a library of multifunctional pyrrolo[1,2-*a*]quinoline skeletons could be efficiently synthesized in a two-step process through an iron(III)-catalyzed three-component coupling of nitro olefines, 1,3-dicarbonyl compounds, and 2-alkynylaniline derivatives followed by a metal-catalyzed intramolecular hydroarylation of the alkyne unit (see Scheme 2). Herein, we report the two-step synthesis of diversely substituted pyrrolo[1,2-*a*]quinolines **A** that involves the iron(III)-catalyzed synthesis of substituted *N*-(2-alkynylaryl)pyrroles **B** followed by a gold(III)-catalyzed intramolecular hydroarylation of the alkyne moiety.

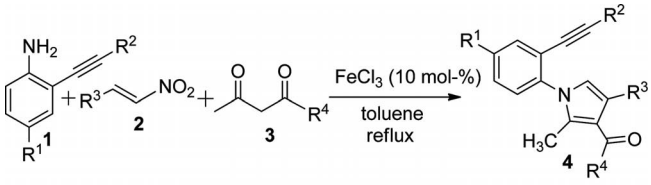
Results and Discussion

First, we developed a simple method to access a large number of functionalized 1-[2-(phenylethynyl)phenyl]-1*H*-pyrroles that would be used in the next step of the synthesis. To do this, we initially used aniline **1a** in our recently developed four-component coupling synthesis of pyrroles.[20d] Only 20% yield of the desired pyrrole derivative **4a** was obtained; however, we observed that **4a** was obtained in 58% yield through a three-component coupling reaction of aniline **1a**, nitroalkene **2a**, and 1,3-dicarbonyl compound **3a** in the presence of $FeCl_3$ (10 mol-%) in toluene at reflux. We tested various other solvents such as dichloroethane, tetrahydrofuran (THF), ethanol, and nitromethane, but they resulted in a lower yield of the desired pyrrole. To improve the yield, various other common Lewis acids such as $InCl_3$, $Yb(OTf)_3$, AgOTf, and $AuCl_3$ were investigated. Unfortunately, all these catalysts gave only a trace amount of the desired product along with many undesired products. Only iron(III) chloride exclusively gave the desired pyrrole **4a** without affecting the alkyne unit. Therefore, we decided to use $FeCl_3$ to catalyze the three-component coupling synthesis of 1-[2-(phenylethynyl)phenyl]-1*H*-pyrroles **4**.

With the optimal conditions in hand, a large number of reactions were examined with various 2-alkynylanilines, nitroalkenes, and 1,3-dicarbonyl compounds in the presence of iron chloride. The results are summarized in Table 1. The reaction proceeded efficiently, and the corresponding products **4b**–**4s** (see Table 1, Entries 2–19) were obtained in moderate to good yields (38–62%). Varying the substituents on any of the components did not have a significant effect. With respect to the anilines, the reaction worked well with a *para* substituent on the aryl ring such as a fluoro, chloro, or methyl group to give comparable yields of the desired pyrroles (see Table 1, Entries 3, 5, and 10). Interestingly, this multicomponent coupling reaction proceeded in the presence of different alkynyl units, and the electronic nature of the substituents on the aryl ring of the alkyne moiety did not have much of an effect on the reaction. All the electron-donating and electron-withdrawing substituents on the aryl ring such as a *p*-OMe, *p*-Br, *p*-Me, *p*-Cl, *p*-CO_2Et, and *m*-NO_2 groups smoothly underwent the reaction to give the corresponding products in moderate to good yields (see Table 1, Entries 8, 9, and 11–14). The anilines that contained alkyne units with alkyl substituents such as cyclohexyl and *n*-hexyl also underwent the reaction to give moderate yields of **4r** and **4s** (see Table 1, Entries 18 and 19). Moreover, varieties of β-aryl- and β-heteroaryl-substituted nitroalkenes were suitable substrates for this coupling reaction. With respect to 1,3-dicarbonyl compounds, acetylacetone (**3a**) and ethyl acetoacetate (**3b**) were tested to give the desired pyrrole derivatives in moderate to good yields. So, the variation of substituents on all the components were comfortably accommodated, thereby securing simple access to the library of multisubstituted 1-[2-(phenylethynyl)-phenyl]-1*H*-pyrroles **4a**–**4s**.

After having the large array of substituted 1-[2-(phenylethynyl)phenyl]-1*H*-pyrroles **4a**–**4s** in hand, we then investigated the second key step, that is, the hydroarylation reaction with a variety of Lewis acids. Intramolecular hydroarylation reactions are generally carried out with many different transition metals such as Pt, Fe, Ga, Ag, In, Ru, and Au.[20] As part of our continuing efforts towards the development iron catalysis, we first examined the cycloisomerization of *N*-(2-alkynylaryl)pyrrole **4a** in the presence of 5 mol-

Table 1. Iron(III)-catalyzed three-component coupling reaction to synthesize substituted 1-[2-(phenylethynyl)phenyl]-1*H*-pyrroles.[a]

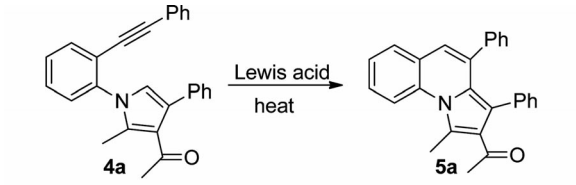


Entry	1 (R^1, R^2)	2 (R^3)	3 (R^4)	Product	Time [h]	Yield [%]
1	H, Ph **1a**	Ph **2a**	CH_3 **3a**	**4a**	7	58
2	**1a**	*p*-Cl-Ph **2b**	**3a**	**4b**	8	56
3	F, Ph **1b**	**2a**	**3a**	**4c**	8	60
4	**1a**	**2a**	C_2H_5O **3b**	**4d**	7	48
5	Cl, Ph **1c**	**2a**	**3a**	**4e**	8	56
6	**1a**	**2a**	Ph **3c**	**4f**	14	56
7	**1a**	*p*-$H_3COC_6H_4$ **2c**	**3b**	**4g**	11	48
8	H, *p*-$H_3COC_6H_4$ **1d**	**2a**	**3a**	**4h**	15	50
9	H, *p*-BrC_6H_4 **1e**	2a	**3a**	**4i**	12	62
10	CH_3, Ph **1f**	**2a**	**3a**	**4j**	12	57
11	H, *p*-$H_3CC_6H_4$ **1g**	**2a**	**3a**	**4k**	14	57
12	H, *p*-ClC_6H_4 **1h**	**2a**	**3a**	**4l**	18	58
13	H, *p*-$EtO_2CC_6H_4$ **1i**	**2a**	**3a**	**4m**	18	55
14	H, *m*-$O_2NC_6H_4$ **1j**	**2a**	**3a**	**4n**	16	45
15	**1a**	2-thiophenyl **2d**	**3a**	**4o**	13	46
16	**1a**	2-Furyl **2e**	**3a**	**4p**	18	45
17	**1a**	2-naphthyl **2f**	**3a**	**4q**	11	42
18	H, cyclohexyl **1k**	**2a**	**3a**	**4r**	13	40
19	H, *n*-hexyl **1l**	**2a**	**3a**	**4s**	14	38

[a] Reagents and conditions: Aniline **1** (1.3 mmol), nitroalkene **2** (1 mmol), and 1,3-dicarbonyl compound **3** (1 mmol).

% $FeCl_3$ in toluene at reflux. Surprisingly, after heating at reflux for 24 h, the desired pyrrolo[1,2-*a*]quinoline **5a** was not formed in even a trace amount (see Table 2, Entry 1), although iron has been shown to be a useful catalyst for various intramolecular hydroarylation reactions. Use of a more polar solvent such as nitromethane or a high-boiling solvent such xylene could not alter the results (see Table 2, Entries 2 and 3). Therefore, we investigated other soft π-Lewis acid catalysts, which could activate alkynes, such as $In(OTf)_3$ (TfO = trifluoromethanesulfonate), AgOTf, and $AuCl_3$. $In(OTf)_3$ (5 mol-%) gave 74% yield of the desired product **5a** when the reaction mixture was heated at reflux in toluene for 20 h, whereas AgOTf (5 mol-%) produced **5a** in 62% yield by using similar conditions for 18 h (see Table 2, Entries 4 and 5). Finally, we noticed that $AuCl_3$ (5 mol-%) was the most effective catalyst for this cyclization process and gave the desired product **5a** in 82% yield when the reaction mixture was heated at reflux for 12 h (see Table 2, Entry 7). Solvents such as nitromethane and xylene with the $AuCl_3$ catalyst lowered the yields of the desired products (see Table 2, Entries 8 and 9). Therefore, we decided to use the Au^{III} catalyst and toluene as the solvent for all the hydroarylation reactions.

Table 2. Optimization of the reaction conditions for the Lewis acid mediated hydroarylation reactions.[a]

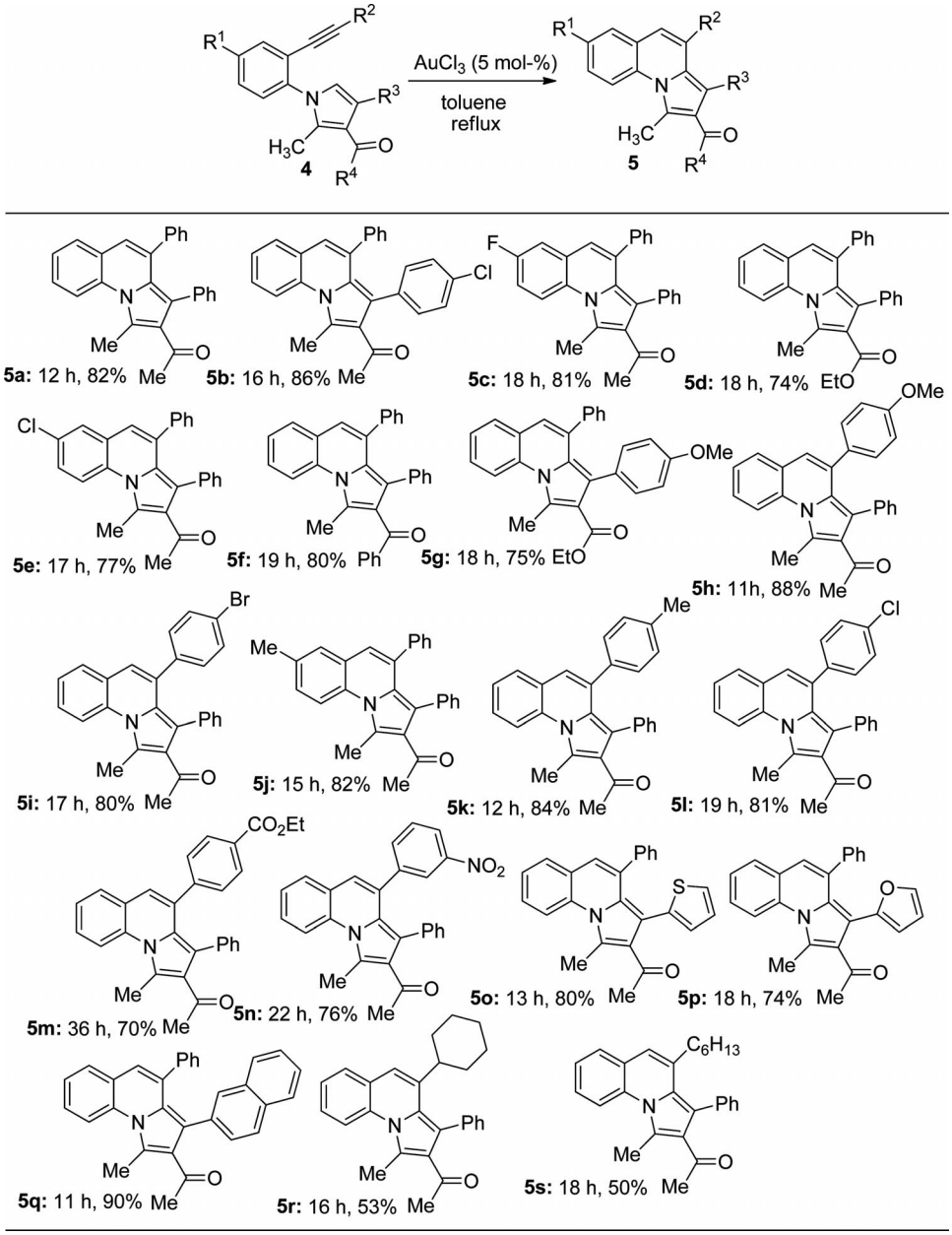


Entry	Catalyst	Solvent	Time [h]	Yield [%][b]
1	$FeCl_3$ (5 mol-%)	toluene	24	0
2	$FeCl_3$ (5 mol-%)	nitromethane	24	0
3	$FeCl_3$ (5 mol-%)	xylene	24	0
4	$In(OTf)_3$ (5 mol-%)	toluene	20	74
5	AgOTf (5 mol-%)	toluene	18	62
6	$AuCl_3$ (2 mol-%)	toluene	22	55
7	***$AuCl_3$ (5 mol-%)***	***toluene***	***12***	***82***
8	$AuCl_3$ (5 mol-%)	nitromethane	24	32
9	$AuCl_3$ (5 mol-%)	xylene	18	61

[a] Reagents and conditions: Substrate **4a** (1 mmol), solvent (2 mL), heating at reflux. [b] Isolated product.

The optimized conditions were then applied to various 1-[2-(phenylethynyl)phenyl]-1*H*-pyrroles to synthesize a diverse range of multifunctionalized pyrrolo[1,2-*a*]quinoline derivatives. The results are summarized in Table 3. A variety of substituents that were attached to the alkyne moiety were studied. To our delight, arylalkynes that contain electron-donating groups such as –OMe and –Me (see Table 3, compounds **5h** and **5k**) or electron-donating groups such as –Br, –Cl, $–CO_2Et$, and $–NO_2$ (see Table 3, compounds **5i** and **5l**–**5n**) persisted under the reaction conditions to give the desired products efficiently in very high yields. Moreover, substituents directly attached to the aryl ring were studied. A weakly electron-donating group such as –Me (see Table 3, compound **5j**) or a weakly electron-withdrawing group such as –F and –Cl (see Table 3, compounds **5c** and **5e**) also gave the desired products in high yields. The –Cl, –Br, $–CO_2Et$, and $–NO_2$ functional groups would be useful for further synthetic transformations to obtain very complex molecules. In addition, the sensitive furan and thiophene heterocyclic molecules, which were attached to

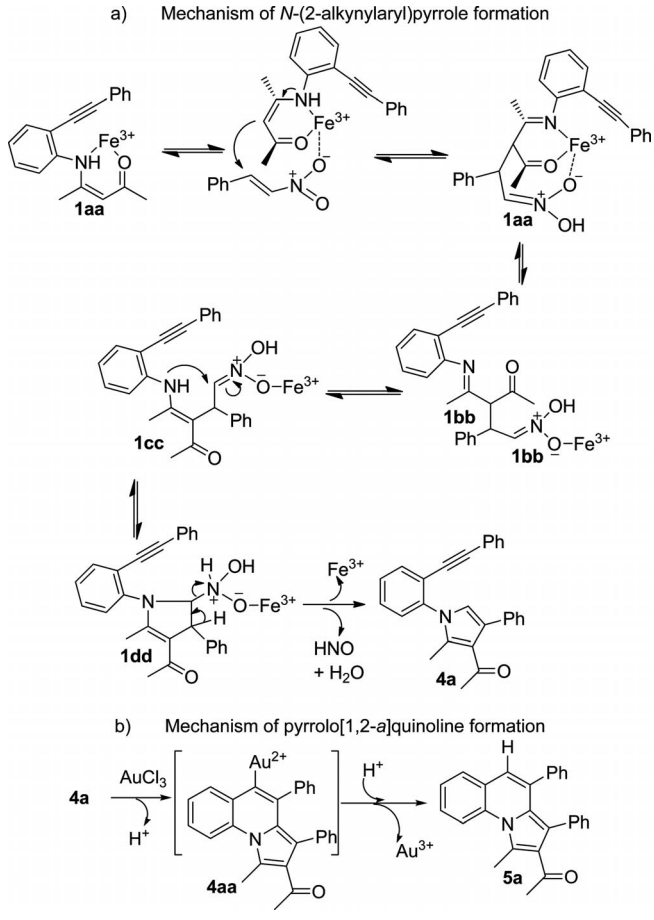
Table 3. Intramolecular alkenylaion to synthesize varieties of multifunctional pyrrolo[1,2-*a*]quinolines.



the pyrrole unit, persisted under the reaction conditions to afford the hybrid heterocyclic molecules **5o** and **5p** in 80% and 74%, respectively. Interestingly, these reaction conditions were also sufficiently efficient for the cyclization of an alkyl-substituted alkyne unit to furnish substituted pyrrolo[1,2-*a*]quinoline **5r** and **5s** in moderate yields of 53% and 50%, respectively. With regard to the *N*-aryl group, no significant electronic effect from the substituted aryl group was observed for this cyclization reaction. Moreover, both a carbonyl and ester group attached to the pyrrole unit were equally tolerated and gave a high yield of the desired cyclized product.

Finally, the hydroarylation reaction of all the above substrates proceeded through a 6-*endo-dig* cyclization to produce the pyrrolo[1,2-*a*]quinoline derivatives. None of the 1-[2-(phenylethynyl)phenyl]-1*H*-pyrrole derivatives underwent cyclization through a 5-*exo-dig* mode. The products were characterized by comparing the ^{1}H NMR spectroscopic data of related structures.[12c] Furthermore, the 6-*endo-dig* mode of cyclization was further confirmed by the ^{1}H NMR spectroscopic data of **5r** and **5s**. In the ^{1}H NMR spectra, the signal of the alkenyl hydrogen atom of the quinoline ring appears at δ = 6.79 (s) ppm for **5r** and at δ = 6.73 (s) ppm for **5s**. The appearance of a singlet peak could only be explained by a 6-*endo-dig* mode of cyclization. If the reaction proceeded through a 5-*exo-dig* cyclization, then those hydrogen atoms would have appeared as a doublet or multiplet.

A possible mechanism based on our previous results and those reported by others is proposed in Scheme 3. First, enamine **1aa** is formed by the reaction between 2-alkynylaniline **1a** and acetylacetone (**3a**) with the catalyst iron(III) chloride. Iron(III) chloride is a moderately strong Lewis acid, and its complexation with a carbonyl group of the 1,3-dicarbonyl compound results in an increase in the electrophilicity of the carbonyl carbon atom and, hence, accelerates the formation of the enamine. Then, both enamine **1aa** and nitrostyrene can coordinate simultaneously with the iron(III) chloride to become activated for the Michael addition. This step is very similar to a previously reported mechanism for an iron(III)-catalyzed Michael addition of a 1,3-dicarbonyl compound with a conjugated carbonyl compound.[21] A simple isomerization of Michael addition product **1cc** followed by cyclization and elimination of HNO and H_2O, as occurs in a Nef reaction, produced 1-[2-(phenylethynyl)phenyl]-1*H*-pyrrole **4a**. Although 2-alkynylanilines are prone to cyclize to an indole, iron(III) chloride chemoselectively produced the pyrrole as shown in Scheme 3. This is in contrast to other catalysts such as indium and gold that gave only a trace amount of the pyrrole derivative along with other uncharacterized products. Indium and gold could strongly coordinate with the alkyne unit and produce undesired products such as indoles.[22]



Scheme 3. A probable mechanism.

Next, the second key step reaction was initiated through the coordination of the alkyne unit with gold(III) followed by a nucleophilic attack of the pyrrole ring on the activated carbon–carbon triple bond to produce intermediate **4aa**. Demetalation through a proton exchange released product **5a** and regenerated the catalyst for the next catalytic cycle.

Finally, a preliminary survey of the photophysical activity of a few compounds was carried out. The photophysical properties (as representative examples) are outlined in Figure 1 and Table 4. These compounds exhibited fluorescence in a range from 452 to 465 nm with quantum efficiencies (Φ) that ranged from 0.033 to 0.067. In view of the spectroscopic measurements of **5a**, absorption spectra were recorded in different solvents (see Supporting Information). In different solvents, the characteristic absorption band was observed with the maximum varying between 370 and 400 nm. However, a distinct bathochromic shift of the absorption maxima was observed in water compared to that observed in nonaqueous solvents.

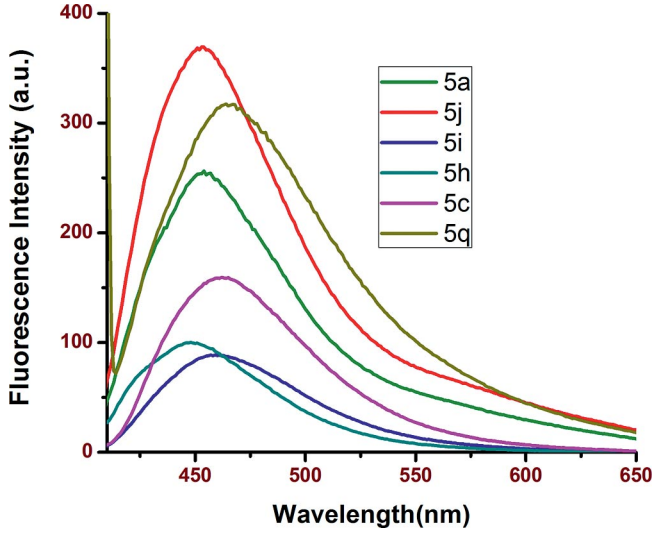


Figure 1. Fluorescence spectra of a few pyrrolo[1,2-*a*]quinoline derivatives in water.

Table 4. Photophysical data of different products in water as solvent.[a]

Compound	λ^{abs}_{max}[b] [nm]	λ^{fl}_{max}[b] [nm]	Φ[c]
5a	375	455	0.056
5c	398	462	0.049
5h	378	448	0.033
5i	370	458	0.032
5j	400	452	0.067
5q	400	465	0.063

[a] Water was used as a solvent for UV/Vis and fluorescence spectra. [b] abs = absorbance, fl = fluorescence. [c] Determined by comparison to a solution of quinine sulfate (Φ = quantum yield).

The shift in magnitude of peak position with regard to the polarity of the medium suggests the ground state of the molecule is more polar. By monitoring the various peaks of absorption maxima of **5a**, we found only emission maxima to show smooth profiles without any vibrational structure. However, the fluorescence of **5a**, which is very sensitive to

the polarity of its surroundings, shows a clear bathochromic shift as the solvent polarity is increased. The bathochromic shift evinces a progressively diminished energy gap between the ground and excited states as a result of the stabilization of the excited state with increasing solvent polarity.

Conclusions

We have demonstrated a concise diversity-orientated approach towards the synthesis of pyrrolo[1,2-*a*]quinoline derivatives through sequential iron(III)-catalyzed three-component coupling followed by gold(III)-catalyzed intramolecular hydroarylation reactions. The present strategy is very simple and efficient and introduces five points of diversity. Many sensitive functional groups and molecules persisted under the reaction conditions. As a result, this strategy provided a library of pyrrolo[1,2-*a*]quinolines from simple starting materials. Furthermore, some of the resulting fused heterocyclic molecules exhibited good fluorescence activity. Because of the ease of availability of the starting materials, this strategy will be useful for the screening of a large number of molecules for biological and photophysical studies to identify potential drug candidates.

Experimental Section

Representative Procedure for the Synthesis of Pyrrole 4a: To a stirred solution of acetylacetone (**3a**, 100 mg, 1 mmol), (2-nitrovinyl)benzene (**2a**, 149 mg, 1 mmol), and 2-(phenylethynyl)aniline (**1a**, 251 mg, 1.3 mmol) in toluene (2 mL) was added anhydrous $FeCl_3$ (16 mg, 0.1 mmol). The mixture was heated to reflux for a set period of time, and then it was cooled to room temperature. The excess amount of solvent was removed under vacuum, and the residue was directly purified by silica gel (mesh 100–200) column chromatography (petroleum ether/EtOAc) to afford **4a** (218 mg, 0.58 mmol, 58%) as a viscous yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 2.37 (s, 3 H), 6.71 (s, 1 H), 7.26–7.31 (m, 5 H), 7.35–7.39 (m, 6 H), 7.46 (dd, J = 6, 4 Hz, 2 H), 7.66 (dd, J = 6, 3.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 30.1, 82.7, 93.0, 113.3, 113.6, 113.7, 114.2, 119.1, 119.6, 119.8, 121.1, 121.4, 126.3, 127.0, 127.8, 127.9, 128.2, 128.3, 130.5, 130.8, 135.0, 135.1, 137.2, 200.0 ppm. HRMS: calcd. for $C_{27}H_{21}NONa$ $[M + Na]^+$ 398.1521; found 398.1539.

Representative Procedure for the Synthesis of Pyrrolo[1,2-*a*]quinoline 5a: To a 10 mL round-bottom flask that contained dry toluene (2 mL) was added compound **4a** (187.5 mg, 0.5 mmol). $AuCl_3$ (7.5 mg, 0.025 mmol) was added, and the reaction mixture was heated to reflux under argon for 12 h. After completion of the reaction (monitored by TLC), toluene was evaporated under reduced pressure, and the residue was purified by silica gel (mesh 100–200) column chromatography (petroleum ether/EtOAc) to afford **5a** (154 mg, 0.41 mmol, 82%) as a yellow solid; m.p. 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3 H), 3.14 (s, 3 H), 6.84–6.86 (m, 3 H), 6.90–7.03 (m, 8 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.49 (t, J = 7.3 Hz, 1 H), 7.64 (d, J = 7.6 Hz, 1 H), 8.44 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 31.8, 117.4, 118.7, 121.9, 124.5, 126.0, 126.1, 126.2, 126.7, 126.8, 127.2, 128.4, 128.6, 128.8, 129.7, 130.8, 133.9, 134.5, 135.7, 138.1, 200.8 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2921, 1656, 1511, 1406, 1369 cm^{-1}. HRMS: calcd. for $C_{27}H_{21}NONa$ $[M + Na]^+$ 398.1521; found 398.1534.

Supporting Information (see footnote on the first page of this article): General methods, representative procedures, ^{1}H and ^{13}C NMR spectra, HRMS data, and absorbance and fluorescence spectra.

Acknowledgments

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[1] a) For review, see: J. P. Michael, *Nat. Prod. Rep.* **1999**, *16*, 675–696; for pharmacologically important indolizines, see: b) Y. Hu, C. Yu, D. Ren, Q. Hu, L. Zhang, D. Cheng, *Angew. Chem.* **2009**, *121*, 5556; *Angew. Chem. Int. Ed.* **2009**, *48*, 5448–5451; c) K.-I. Takao, R. Munakata, K.-I. Tadano, *Chem. Rev.* **2005**, *105*, 4779–4807; d) A. Mieczkowski, V. Roy, L. A. Agrofoglio, *Chem. Rev.* **2010**, *110*, 1828–1856.

[2] a) G. W. Gribble in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky C. W. Rees, E. S. V. Scriven), Pergamon, New York, **1996**, vol. 2, pp. 207–257; b) P. W. Le Quesne, Y. Dong, T. A. Blythe in *Alkaloids: Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Elsevier Science Ltd., Oxford, **1999**, vol. 13, pp. 237–287; c) J. F. Eggler, M. R. Johnson, L. S. Melvin, Eur. Patent Appl. EP 90516, **1983**; d) W. K. Anderson, A. R. Heider, N. Raju, J. A. Yucht, *J. Med. Chem.* **1988**, *31*, 2097–2102; e) D. St. Clair-Black, N. Kumar, *Org. Prep. Proced. Int.* **1991**, *23*, 67–92; f) D. J. Faulkner, *Nat. Prod. Rep.* **1996**, *13*, 75–125; g) J. P. Edwards, R. Higuchi, T. Jones, PCT Int. Patent Appl. WO 9749709, **1997**; h) Q. Ding, K. Chichak, J. W. Lown, *Curr. Med. Chem.* **1999**, *6*, 1–28; i) W. H. Pearson, W.-K. Fang, *J. Org. Chem.* **2000**, *65*, 7158–7174; j) L.-L. Wei, R. P. Hsung, H. M. Sklenicka, A. I. Gerasyuto, *Angew. Chem.* **2001**, *113*, 1564; *Angew. Chem. Int. Ed.* **2001**, *40*, 1516–1518; k) S. M. Weinreb, *Chem. Rev.* **2006**, *106*, 2531–2549.

[3] a) T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly, B. Witkop, *Helv. Chim. Acta* **1974**, *57*, 2597–2604; b) J. W. Daly, B. Witkop, T. Tokuyama, T. Nishikawa, I. L. Karle, *Helv. Chim. Acta* **1977**, *60*, 1128–1140.

[4] a) W. H. Pearson, W. Fang, *J. Org. Chem.* **2000**, *65*, 7158–7174; b) L.-L. Wei, R. P. Hsung, H. M. Sklenicka, A. I. Gerasyuto, *Angew. Chem.* **2001**, *113*, 1564; *Angew. Chem. Int. Ed.* **2001**, *40*, 1516–1518; c) M. Santarem, C. Vanucci-Bacqué, G. Lhommet, *J. Org. Chem.* **2008**, *73*, 6466–6469.

[5] a) M. Mensah-Dwumah, J. W. Daly, *Toxicon* **1978**, *16*, 189–194; b) C. Souccar, W. A. Varanda, R. S. Aronstam, J. W. Daly, E. X. Albuquerque, *Mol. Pharmacol.* **1984**, *25*, 384–394.

[6] a) A. Jossang, H. E. Bitar, V. C. Pham, T. Sévenet, *J. Org. Chem.* **2003**, *68*, 300–304; b) T. Ikeda, T. Yaegashi, T. Matsuzaki, S. Hashimoto, S. Sawada, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 342–345.

[7] J. P. Michael, C. B. Konging, C. D. Hosken, V. T. Stanbury, *Tetrahedron* **2001**, *57*, 9635–9648.

[8] A. Hazra, S. Mondal, A. S. Maity, P. Naskar, R. Saha, K. B. Paira, P. Sahu, S. Paira, C. Ghosh, A. Sinha, A. Samanta, S. Banerjee, N. B. Mondal, *Eur. J. Med. Chem.* **2011**, *46*, 2132–2140.

[9] L. Leontie, I. Druta, R. Danac, G. I. Rusa, *Synth. Met.* **2005**, *155*, 138–145.

[10] a) H. E.-A. El-Sayed, I. El-Sayed, *Adv. Heterocycl. Chem.* **2003**, *84*, 71–190; b) G. Yue, Y. Wan, S. Song, G. Yang, Z. Chen, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 453–458; c) A. V. Butin, F. A. Tsiunchik, V. T. Abaev, K. V. Bosikova, *ARKIVOC* **2009**, 79–87; d) D. Basavaiah, B. Devendar, D. V. Lenin, T. Satyanarayana, *Synlett* **2009**, 411–416; e) M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Synthesis* **2008**, 1688–1702; f) A. Cappelli, G. Giuliani, M. Anzini, D. Riitano, G. Giorgi, S. Vomero, *Bioorg.*

Med. Chem. **2008**, *16*, 6850–6859; g) D. T. Jones, A. L. Harris, *Mol. Cancer Ther.* **2006**, *5*, 2193–2202.

[11] a) M. R. Caira, E. Georgescu, F. Georgescu, M. M. Popa, F. Dumitraşcu, *ARKIVOC* **2009**, 242–253; b) E. Georgescu, M. R. Caira, F. Georgescu, B. Drăghici, M. M. Popa, F. Dumitraşcu, *Synlett* **2009**, 1795–1799; c) E. Georgescu, F. Dumitraşcu, F. Georgescu, C. Drăghici, M. M. Popa, *Rev. Roum. Chim.* **2010**, *55*, 217–221; d) V. Nair, S. Devipriya, E. Suresh, *Synthesis* **2008**, 551.

[12] a) S. Ye, J. Liu, J. Wu, *Chem. Commun.* **2012**, *48*, 5028–5030; b) A. K. Verma, S. P. Shukla, J. Singh, V. Rustagi, *J. Org. Chem.* **2011**, *76*, 5670–5684; c) V. Mamase, A. Furstner, *J. Org. Chem.* **2002**, *67*, 6264–6267; d) D. I. Chai, M. Lautens, *J. Org. Chem.* **2009**, *74*, 3054–3061.

[13] T.-J. Li, H.-M. Yin, C.-S. Yao, X.-S. Wang, B. Jiang, S.-J. Tu, G. Li, *Chem. Commun.* **2012**, *48*, 11966–11968.

[14] a) X.-Y. Liu, C.-M. Che, *Angew. Chem.* **2008**, *120*, 3865; *Angew. Chem. Int. Ed.* **2008**, *47*, 3805–3810; b) Y. Zhou, E. Feng, G. Liu, D. Ye, J. Li, H. Jiang, H. Liu, *J. Org. Chem.* **2009**, *74*, 7344–7348.

[15] a) X. Li, C. Li, W. Zhang, X. Lu, S. Han, R. Hong, *Org. Lett.* **2010**, *12*, 1696–1699; b) T. Aggarwal, S. Kumar, D. K. Dhaked, R. K. Tiwari, P. V. Bharatam, A. K. Verma, *J. Org. Chem.* **2012**, *77*, 8562–8573; c) T. Aggarwal, R. R. Jha, R. K. Tiwari, S. Kumar, S. K. R. Kotla, S. Kumar, A. K. Verma, *Org. Lett.* **2012**, *14*, 5184–5187.

[16] a) D. I. Chai, M. Lautens, *J. Org. Chem.* **2009**, *74*, 3054–3061; b) W. H. Pearson, W. K. Fang, *J. Org. Chem.* **2000**, *65*, 7158–7174.

[17] a) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; b) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; c) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; d) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123–131; e) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831–844.

[18] For review, see: a) V. Mamase, P. Hannen, A. Furstner, *Chem. Eur. J.* **2004**, *10*, 4556–4575; b) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639; c) M. Bandini, E. Emer, S. Tommasi, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2006**, 3527–3544; d) T. Kitamura, *Eur. J. Org. Chem.* **2009**, 1111–1125.

[19] a) A. Arcadi, F. Blesi, S. Cacchi, G. Fabrizi, A. Goggiamani, F. Marinelli, *Org. Biomol. Chem.* **2012**, *10*, 9700–9708; b) K. Komeyama, R. Igawa, K. Takaki, *Chem. Commun.* **2010**, *46*, 1748–1750; c) C. D. Zotto, J. Wehbe, D. Virieux, J.-M. Campagne, *Synlett* **2008**, 2033–2035; d) H. A. Wegner, S. Ahles, M. Neuburger, *Chem. Eur. J.* **2008**, *14*, 11310–11313.

[20] a) K. Bera, S. Sarkar, S. Jalal, U. Jana, *J. Org. Chem.* **2012**, *77*, 8780–8786; b) S. Sarkar, S. Maiti, K. Bera, S. Jalal, U. Jana, *Tetrahedron Lett.* **2012**, *53*, 5544–5547; c) K. Bera, S. Sarkar, S. Biswas, S. Maiti, U. Jana, *J. Org. Chem.* **2011**, *76*, 3539–3544; d) S. Maiti, S. Biswas, U. Jana, *J. Org. Chem.* **2010**, *75*, 1674–1683; e) U. Jana, S. Maiti, S. Biswas, *Tetrahedron Lett.* **2008**, *49*, 858–862; f) U. Jana, S. Biswas, S. Maiti, *Eur. J. Org. Chem.* **2008**, 5798–5800; g) S. Biswas, S. Maiti, U. Jana, *Eur. J. Org. Chem.* **2009**, 2354–2359.

[21] J. Christoffers, *Chem. Commun.* **1997**, 943–944.

[22] For indium- and gold-catalyzed indole formation of 2-alkynylaniline, see: a) N. Sakai, K. Annaka, A. Fujita, A. Sato, T. Konakahara, *J. Org. Chem.* **2008**, *73*, 4160–4165; b) A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* **2004**, 610–618.

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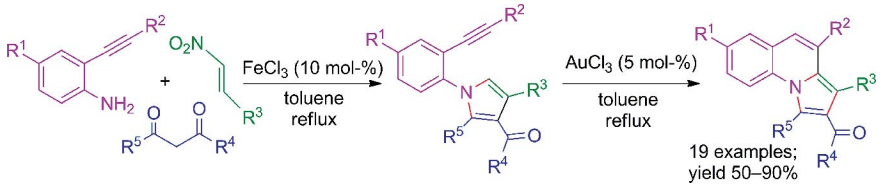
Pyrrolo[1,2-*a*]quinolines



An efficient synthesis of complex pyrrolo[1,2-*a*]quinoline derivatives was achieved by an iron(III)-catalyzed synthesis of *N*-(2-alkynylaryl)pyrroles followed by a gold(III)-catalyzed intramolecular hydroarylation reaction. The availability of the starting materials and the generality of the reaction sequences make it an attractive strategy to synthesize a diverse range of pyrrolo[1,2-*a*]quinoline derivatives.

Keywords: Nitrogen heterocycles / Iron / Gold / Multicomponent reactions / Cyclization / Fluorescence

