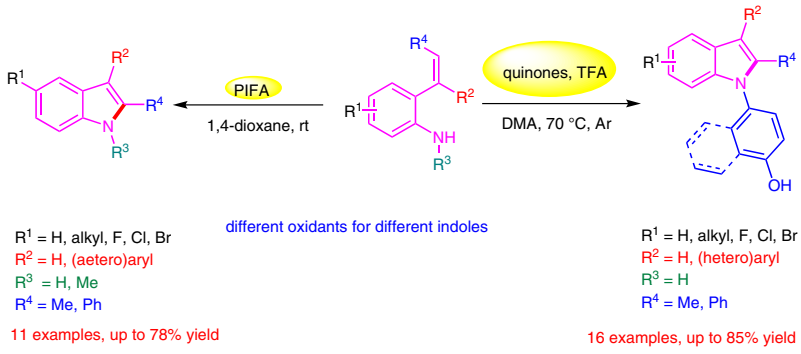
Synlett M. Wu, R. Yan Letter

Synthesis of Indoles from 2-Vinylanilines with PIFA or TFA and Quinones

Mingzhong Wu
Rulong Yan*

State Key Laboratory of Applied Organic Chemistry, Key laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou 730000, Gansu, P. R. of China
yanrl@lzu.edu.cn



Received: 10.10.2016
Accepted after revision: 25.11.2016
Published online:
DOI: 10.1055/s-0036-1588122; Art ID: st-2016-w0679-l

Abstract The cyclizations involved in the synthesis of different indoles from 2-vinylanilines with PIFA {[bis(trifluoroacetoxy)iodo]benzene} and quinones have been developed under mild conditions. Various substituents on 2-vinylanilines induced good compatibility and gave the desired products in moderate to good yields.

Keywords 2-vinylanilines, PIFA, quinones, oxidant, indoles

Indoles, as one of the most important and valuable heterocycles, are prevalent in the activation of biological activities, medical chemistry, and material sciences.[1] In addition, the indole moiety is also a key intermediate for many organic synthesis.[2] In view of these benefits, a number of different methods for the synthesis of indole derivatives have been developed in the past several years.[3] The predominant strategy relies on the transition-metal-catalyzed coupling reactions to build new C–N bonds for the rapid access to useful indole derivatives.[4] When this approach was reported by the research group of Hegedus, the Pd(II)-catalyzed C–H amination of 2-vinylanilines has been considered as an effective pathway toward the production of the indole skeleton (Scheme 1, a).[5] Zheng and co-workers reported a new type of reactivity of nitrogen-centered radical cations for the synthesis of indoles (Scheme 1, b).[6] Recently, Youn and co-workers, showed an operationally effective and straightforward metal-free C–H amination able to afford a broad range of substituted indoles.[7] Nevertheless, the search for sustainable and more efficient methods for the preparation of indoles is of constant interest.[8] In this paper, we communicate metal-free methods for the synthesis of different indoles from 2-vinylanilines with different oxidants PIFA and quinones.

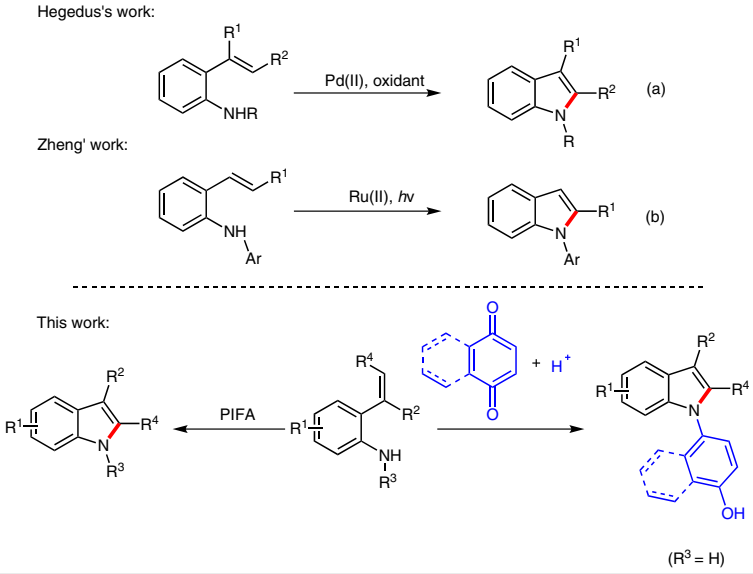
As a starting point for the development of our direct amination, we initially used 2-(1-phenylvinyl)aniline (**1a**) as the test substrate for optimizing the reaction conditions (Table 1). Originally, iodosobenzene (PhIO) was employed as the oxidant.

Table 1 Optimization of the Reaction Conditions[a]

1a **2a**

Entry	Oxidant	Solvent	Yield (%)
1	PhIO[b]	MeCN	40
2	PhIO	MeCN	43
3	DMP	MeCN	12
4	$I_2 + K_2S_2O_8$	MeCN	-
5	PIDA	MeCN	58
6[c]	PIDA	MeCN	60
7[c]	DDQ	MeCN	51
8	PIFA	MeCN	62
9	PIFA	DMF	42
10	PIFA	EtOH	45
11	PIFA	DCE	62
12	PIFA	THF	74
13	PIFA	toluene	50
14	**PIFA**	**1,4-dioxane**	**78**

[a] Reaction conditions: **1a** (0.3 mmol), oxidant (0.36 mmol), solvent (1 mlL), 1.5 h, r.t.
[b] The reaction was carried out at 70 °C for 24 h.
[c] Amount of AcOH used was 20 mol%.

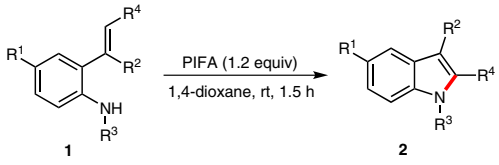


Scheme 1 Typical routes and our strategy for the synthesis of substituted indoles

Using PhIO (1.2 equiv) in methyl cyanide (MeCN) and leaving the reaction mixture at 70 °C, produced the desired product in 40% yield, although, even after 24 hours, the reaction was not completed (Table 1, entry 1). The temperature was optimized and the results indicated that the best yield was obtained at room temperature to afford the indole in 43% yield (Table 1, entry 2). Then, various oxidants were evaluated and the results revealed that PIFA was the most effective oxidant by producing the compound **2a** in 62% yield (Table 1, entries 1–8). The screening of different solvents, *N*,*N*-dimethylformamide (DMF), ethanol, 1,2-dichloroethane (DCE), tetrahydrofuran (THF), toluene and 1,4-dioxane, showed that 1,4-dioxane provided the best yield (Table 1, entries 9–14). We further determined that either reducing or increasing the amount of PIFA led to lower yields of **2a**. The optimized conditions were then established and are shown in Table 1 (entry 14).

Under the optimized conditions, a wide range of 2-vinylanilines were examined and the results are summarized in Table 2.[9] The electron-withdrawing and electron-donating groups on the aromatic ring and nitrogen atom of 2-vinylanilines were compatible and gave the desired products in moderate to good yields. Alkenes with different R^2 and R^3 groups were also employed to generate the corresponding substituted indoles in 73% and 68% yields, respectively (Table 2, entries 6 and 7). Subsequently, diverse substituents on the aromatic and vinyl moieties of 2-vinylanilines were also investigated, which led to the desired products **2h** and **2i** in 63% and 57% yields, respectively (Table 2, entries 8 and 9). Unfortunately, the substrates of α,β-disubstituted and α,α,β-trisubstituted were not tolerated in this transformation and the desired products **2j** and **2k** were not isolated.

Table 2 Synthesis of Indole Derivatives with 2-Vinylanilines and PIFA



1 2

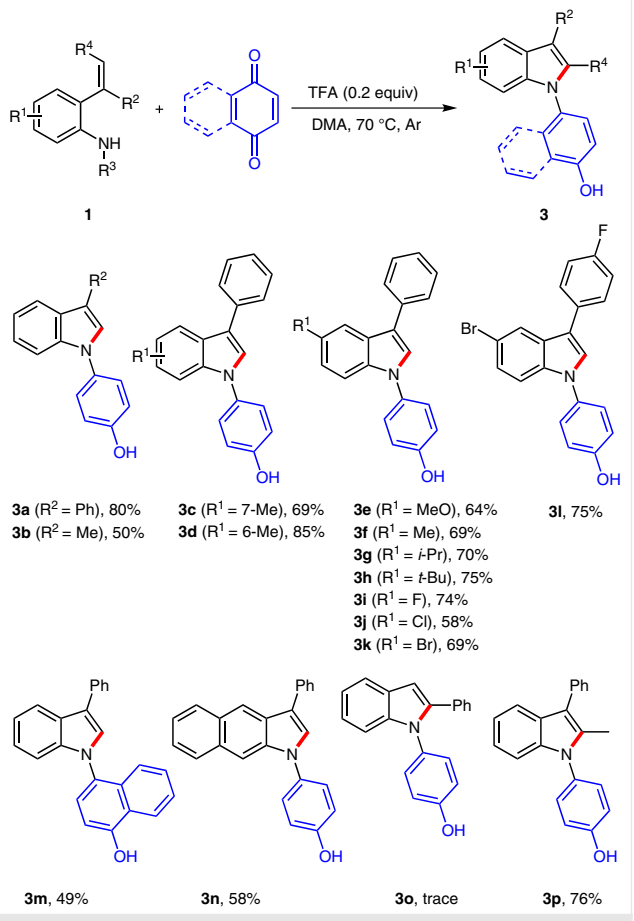
Entry	R^1	R^2	R^3	R^4	Yield (%)[a]
1	H	Ph	H	H	78 (**2a**)
2	Me	Ph	H	H	64 (**2b**)
3	*i*-Pr	Ph	H	H	63 (**2c**)
4	*t*-Bu	Ph	H	H	71 (**2d**)
5	F	Ph	H	H	56 (**2e**)
6	H	4-MeC_6H_4	H	H	73 (**2f**)
7	H	Ph	Me	H	68 (**2g**)
8	Br	4-FC_6H_4	H	H	63 (**2h**)
9	Cl	4-ClC_6H_4	H	H	57 (**2i**)
10	H	H	H	Ph	– (**2j**)
11	H	Ph	H	Me	trace (**2k**)

[a] Yields of isolated products.

In the course of optimizing the experimental conditions, different indoles were detected when the oxidant benzoquinone was used. The product 4-(3-phenyl-1*H*-indol-1-yl)phenol (**3a**) was produced with 2-(1-phenylvinyl)aniline (**1a**) and benzoquinone in the presence of acetic acid (AcOH) as catalyst. Subsequently, we extensively screened acids, solvents, and other factors under argon. The results are summarized in Table S1 (Supporting Information). The highest yield of **3a** was achieved when the reac-

tion was carried out with **1a** and benzoquinone (1.2 equiv), trifluoroacetic acid (TFA; 20 mol%) in *N*,*N*-dimethylacetamide (DMA) at 70 °C under argon (Table S1, entry 13).

Next, we investigated the reaction scopes under the optimized conditions to synthesize indoles and the results are listed in Scheme 2.[10] As shown in Scheme 2, the anilines carrying an *ortho*-terminal alkene (R^2 = Me, Ph) produced the *N*-arylindoles **3a** and **3b** in moderate yields. Moreover, the reaction was not significantly affected by the nature of the groups of the aromatic ring of 2-vinylanilines. The *ortho*, *meta*, and *para* positions of the substituents of the substrates did not have a considerable effect on the efficiency of the reaction. For example, the 2-vinylanilines presenting methyl group could afford the desired products **3c** and **3d** in 69% and 85% yields, respectively. The reaction with naphthalene-1,4-dione was also satisfactory by producing **3m** in 49% yield. The product *N*-arylindole **3n** could also be obtained in 58% yield. Particularly, 2-(1-phenylprop-1-en-1-yl)aniline could react with benzoquinone to give **3p** in 76% yield. Nevertheless, the reaction was incompatible with 2-styrylaniline, and failed to give the desired product **3o**.



Scheme 2 Synthesis of indoles with 2-vinylanilines and quinones

■■*include discussion of Figure 1*■■

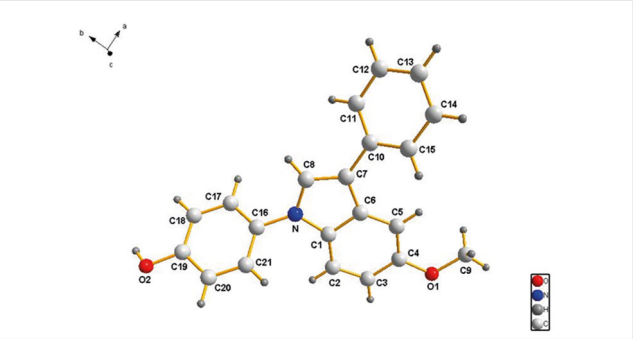


Figure 1 X-ray crystal structure of *N*-arylindole **3e**

On the basis of the results described above, a plausible mechanism pathway accounting for the conversion of these two pathways is proposed in Scheme 3. One of the routes describes the formation of the iodo intermediate **4** from the reaction of the substrate **1a** with PIFA by releasing trifluoroacetic acid. Then an intramolecular electrophilic cyclization occurs on **4**, with the release of one molecule each of iodobenzene, and trifluoroacetate acid, which leads to the formation of the 3-phenyl-1*H*-indole (**2a**). Similarly, the other route involves the reaction of the substrate **1a** with the protonated benzoquinone to produce the imine **5**. Intramolecular electrophilic addition of the imine **5** forms the intermediate **6**. Finally, the desired product **3a** is generated by the proton elimination.

In conclusion, we have developed a novel and metal-free method to easily prepare different indoles from 2-vinylanilines with PIFA, or with TFA and quinones■■*changes OK? PIFA not used with quinones*■■. In this study, various substituted groups of 2-vinylanilines reacted smoothly and produced the desired indoles in moderate to good yields.

Acknowledgment

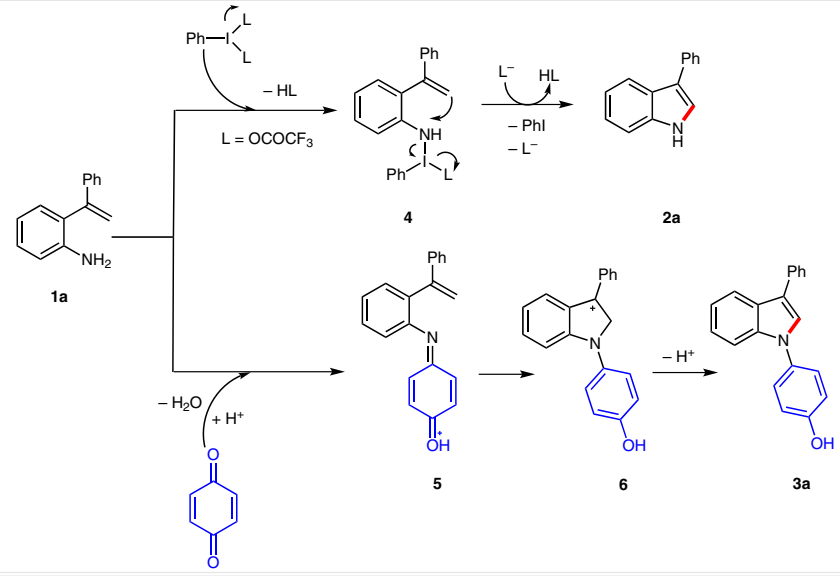
This work was supported by the National Natural Science Foundation of China (21672086, 21202067), the Gansu Province Science Foundation for Youths (1606RJYA260) and the Fundamental Research Funds for the Central Universities (lzujbky-2016-39).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588122.

References and Notes

(1) (a) Kochanowska, K. A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (b) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491. (c) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761. (d) Kaushik, N.; Attri, P.; Kumar, N.; Kim, C.; Verma, A.; Choi, E. *Molecules* **2013**, *18*, 6620.



Scheme 3 Proposed catalytic cycle

(2) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302. (b) Sheppard, T. D. *Org. Biomol. Chem.* **2009**, *7*, 1043. (c) Kambe, N.; Iwasaki, T.; Terao, J. *J. Chem. Soc. Rev.* **2011**, *40*, 4937.

(3) (a) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508. (b) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J. C. *Chem. Soc. Rev.* **2012**, *41*, 3929. (c) Hegedus, L. S. *Angew. Chem. Int. Ed.* **1988**, *27*, 1113. (d) Inman, M.; Moody, C. *J. Chem. Sci.* **2013**, *4*, 29. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, 215.

(4) (a) Daugulis, O.; Do, H. Q.; Shabashov, D. A. *Chem. Res.* **2009**, *42*, 1074. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (c) Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.-X. *J. Org. Chem.* **2008**, *73*, 8639. (d) Taillefer, M.; Xia, N.; Ouali, A.; Wang, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 934. (e) Taillefer, M.; Xia, N.; Ouali, A.; Wang, A. *Angew. Chem. Int. Ed.* **2007**, *119*, 952. (f) Youn, S. W.; Ko, T. Y.; Jang, M. J.; Jang, S. S. *Adv. Synth. Catal.* **2015**, *357*, 227.

(5) (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. (b) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. (c) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335. (d) Fra, L.; Millán, A.; Souto, J. A.; Muñiz, K. *Angew. Chem. Int. Ed.* **2014**, *126*, 7477. (e) Fra, L.; Millán, A.; Souto, J. A.; Muñiz, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 7349. (f) Youn, S. W.; Lee, S. R. *Org. Biomol. Chem.* **2015**, *13*, 4652. (g) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. (h) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14048. (i) Gu, Z.-Y.; Liu, C.-G.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2016**, *18*, 2379. (j) Liwosz, T. W.; Chemler, S. R. *Chem. Eur. J.* **2013**, *19*, 12771.

(6) Maity, S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9562.

(7) Jang, Y. H.; Youn, S. W. *Org. Lett.* **2014**, *16*, 3720.

(8) (a) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764. (b) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem. Int. Ed.* **2011**, *123*, 8508. (c) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8358. (d) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (e) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *121*, 9786. (f) Modha, S. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2015**, *137*, 1416.

(9) **General Procedure for the Synthesis of Substituted Indoles from 2-Vinylanilines with Oxidant PIFA**: The 2-(1-phenylvinyl)aniline (**1a**; 0.2 mmol) and PIFA (2.4 mmol) were added weighed into a 10-mL vial equipped with a magnetic stir bar. 1,4-dioxane (1 mL) was added, and this mixture was stirred under air. After being stirred at r.t. for 1.5 h, the solvent was evaporated in vacuum and the crude product was purified by column chromatography, eluting with petroleum ether–EtOAc (10:1) to afford the desired product **2a** as a colorless solid (32 mg, 78% yield); mp 75–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (br s, 1 H), 7.93–7.95 (d, *J* = 8.0 Hz, 1 H), 7.64–7.67 (m, 2 H), 7.41–7.45 (m, 2 H), 7.33–7.35 (d, *J* = 8.0 Hz, 1 H), 7.16–7.29 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.72, 135.64, 128.87, 127.56, 126.07, 125.79, 122.48, 121.90, 120.41, 119.88, 118.32, 111.52. HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N$: 194.0964; found: 194.0960.

(10) **General Procedure for the Synthesis of Indole Derivatives from 2-Vinylanilines with Oxidant Quinones**: The 2-(1-phenylvinyl)aniline (**1a**; 0.2 mmol), benzoquinone (1.2 equiv) and TFA (0.2 equiv) were added weighed into a 10-mL vial equipped with a magnetic stir bar, and DMA (1 mL) was added, this mixture was stirred under Ar. After being stirred at 70 °C for 5 h, the reaction mixture was cooled to r.t. and then extracted with EtOAc (3 × 15 mL). The combined organic phase was dried over anhyd Na_2SO_4. The solvent was evaporated in vacuum and the crude product was purified by column chromatography, eluting with petroleum ether–EtOAc (10:1) to afford the desired product **3a** as a light pink solid; yield: 34 mg (80%); mp 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–8.00 (m, 1 H), 7.69–7.72 (m, 2 H), 7.42–7.48 (m, 4 H), 7.35–7.39 (m, 2 H), 7.21–7.32 (m, 3 H), 6.93–6.95 (d, *J* = 8 Hz, 2 H), 5.24 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.74, 135.59, 134.62, 132.26, 129.09, 127.82, 127.59, 127.18, 127.07, 126.51, 126.32, 122.95, 119.58, 118.22, 116.46, 111.96. HRMS: *m*/*z* [M + H]$^+$

calcd for $C_{20}H_{16}NO$: 286.1227; found: 286.1225.

4-(5-Methoxy-3-phenyl-1*H*-indol-1-yl)phenol (3e): light pink solid; yield: 25 mg (64%); mp 89–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.94 (br s, 1 H), 6.96 (s, 1 H), 6.90–6.92 (d, *J* = 8.0 Hz, 2 H), 6.54–6.65 (m, 6 H), 6.42–6.46 (m, 1 H), 6.14–6.16 (d, *J* = 8.0 Hz, 2 H), 6.04–6.06 (m, 1 H), 2.98 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.74, 155.05, 135.60, 132.11, 130.90, 129.43, 127.66, 127.28, 126.91, 126.23, 126.05, 117.07, 116.65, 112.84, 112.11, 101.71, 55.92. HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}NO$: 285.1148; found: 285.1144. ■■*HRMS not for* ***3e****?*■■