COMMUNICATIONS

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Sulfur-Assisted and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-Catalyzed Cyclization of 2-Alkynylanilines for the Metal-Free Synthesis of Indole Derivatives

Hongwei Zhou,[a,]* Da Zhu,[a] Yanpeng Xing,[a] and Huafeng Huang[a]

[a] Department of Chemistry, Zhejiang University (Campus Xixi) , Hangzhou 310028, People's Republic of China
Fax: (+ 86)-571-8892-0271; e-mail: zhouhw@zju.edu.cn

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This paper is dedicated to the memory of Prof. Xian Huang.

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Abstract: A sulfur-assisted and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)-catalyzed cyclization of 2-alkynylanilines for the metal-free synthesis of indole derivatives is reported. As a result of the metal-free process, the ready availability of the starting materials and the simple and convenient operation, the type of reaction presented here has potential utility in organic synthesis. A 10-gram scale preparation may demonstrate the possibility of its application in the environmentally friendly synthesis of indole derivatives.

Keywords: cyclization; DBU-catalyzed reaction; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); indole derivatives; metal-free conditions; sulfur-assisted recation

Indoles may be one of the most important heterocyclic compounds which exhibit a variety of biological activities.[1] Due to their applications in pharmaceutical fields, investigations on the development of efficient preparative methods for indole derivatives have continuously attracted the attention of organic chemists. Many powerful methodologies for the synthesis of these heterocycles have been developed, including the Fischer indole synthesis,[2] cyclization of 2-alkynylanilines,[3] a metal-catalyzed cascade reaction,[4] and intramolecular C−H amination of azidoacrylates.[5] In the above methodologies, cyclization of 2-alkynylanilines promoted by the transition metals or metal salts (Lewis acids) is widely used because of the readily available starting materials and reagents.

During our research, we tried to prepare a particular substrate – 1-butyl-2-(phenylsulfinylmethyl)indole – for conducting a Prummerer reaction, which might be prepared *via* a classic oxidization of 1-butyl-2-(phenylthiomethyl)indole. However, using *N*-butyl-2-[3-(phenylthio)prop-1-ynyl]aniline (**1a**) as the starting material,[6] we failed to obtain the expected 1-butyl-2-(phenylthiomethyl)indole *via* Lewis acids- or Pd-promoted approaches,[3f,4b] probably because the presence of the sulfur atom is harmful to the Pd and Lewis acids. Although the cyclizations of 2-alkynylanilines in the presence of excesses of strong bases, such as *t*-BuOK, EtONa, CsOH or NaOH, were documented,[7] we only obtained sluggish results, which were unsuitable to the large-scale preparation.

Based on our previous understanding of the sulfur-assisted propargyl-allenyl isomerization,[8] we proposed an allene intermediate *N*-butyl-2-[3-(phenylthio)propa-1,2-dienyl]aniline, which could be easily produced *in situ* by **1a** in the presence of a suitable base, to reach our expected product. The allene moiety could be thought of as an "activated olefin", which may enhance the cyclization possibility compared with that of the thermodynamically more stable alkyne.

This proposal stimulated us to investigate the possibility of a base-promoted cyclization of **1a** to access 1-butyl-2-(phenylthiomethyl)indole (**2a**) without transition metals or Lewis acids (Figure 1).

As a first attempt, we initiated our study by treating **1a** with various bases and examining the solvent effect. Weak inorganic bases such as K_2CO_3 or triethylamine could not trigger the reaction whereas strong bases *t*-BuOK and EtONa gave low yields. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) gave the expected **2a** in good yields at various reaction temperatures (Table 1).

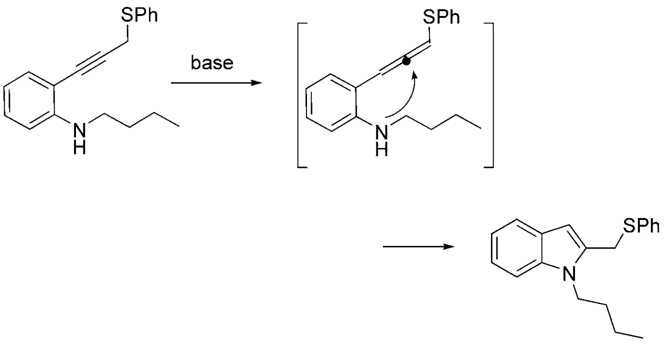
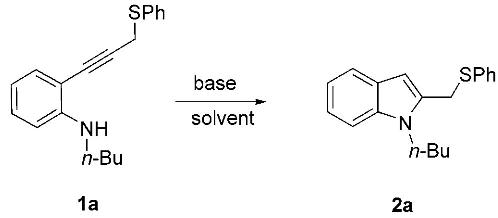


Figure 1. Proposal of the cyclization *via* an allene intermediate.

Table 1. Base and solvent effects.[a]



Entry	Base	Solvent	Time [h]	Temp. [°C]	Yield of **2a**
1	Et_3N	toluene	24	reflux	NR
2	Et_3N	THF	24	reflux	NR
3	Et_3N	MeCN	24	reflux	NR
4	K_2CO_3	MeCN	24	reflux	NR
5	*t*-BuOK	NMP	12	r.t.	35%
6	EtONa	NMP	12	50	32%
7	DBU	toluene	24	r.t.	NR
8	DBN	THF	12	reflux	42%
9	DBN	MeCN	12	60	34%
10	DBN	toluene	12	90	76%
11	DBU	THF	24	r.t.	NR
12	DBU	toluene	12	60	75%
13	DBU	THF	12	reflux	58%
14	DBU	MeCN	12	60	38%
15	DBU	toluene	12	90	**84%**

[a] Substrate **1a** (0.5 mmol) and base (0.6 mmol) in solvent (1 mL) under an N_2 atmosphere.

Although stoichiometric DBU gave an acceptable result, a catalytic dosage of DBU would make this reaction environmentally friendly and useful for large-scale preparation. Thus, we examined the reaction in the presence of 0.3 equiv., 0.1 equiv. and 0.05 equiv. of DBU, respectively; 0.3 equiv. of DBU gave a similar result to 1.2 equiv. and 0.05 equiv. required 70 h for the completion. Catalyzed by 0.1 equiv. of DBU the reaction offered 86% yield and went to completion in 30 h.

With this result in hand, we examined the scope of the reaction and obtained the expected indoles in good yields under mild conditions (Table 2).

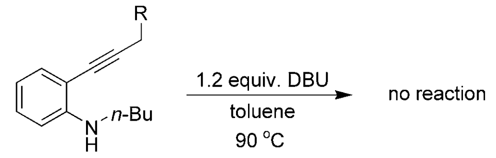
Although we did not detect the allene intermediate shown in Figure 1, we conducted control experiments which might be helpful for supporting the pathway proposed. We firstly prepared *N*-butyl-2-(3-phenoxyprop-1-ynyl)aniline (**3**) and *N*-butyl-2-(oct-1-ynyl)aniline (**4**) for replacing the sulfur by oxygen and carbon, respectively, and conducted the reactions under the same conditions. Only the starting materials were recovered, illustrating that the sulfur atom might play a role in this reaction (Scheme 1).

Then we synthesized *N*-butyl-2-[3-methyl-3-(phenylthio)but-1-ynyl]aniline (**5**) as the substrate to examine the reaction, in which the propargyl-allenyl isomerization was prevented. We recovered **5** in 86% yield, showing that the allene intermediate is essential for the cyclization (Scheme 2).

As a simple and efficient route to indole derivatives, the usefulness of this synthetic method should be demonstrated on a multi-gram scale preparation. We thus ran the cyclization of **1a** on a 10-gram scale and obtained **2a** in a yield of 86%. For the original purpose of preparation of 1-butyl-2-(phenylsulfinylmethyl)indole (**6**), we oxidized **2a** using $NaIO_4$ as the oxidant and obtained **6** in a satisfactory yield (Scheme 3).

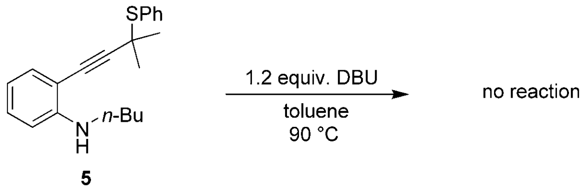
(Arylmethyl)(phenyl)sulfane derivatives, containing an acidic methylene group and a sulfur atom, could be used in the transformations such as reduction,[9] oxidation to sulfone,[10] alkylation[11] and acylation[12] of the sulfane group. Thus, it may be reasonably envisioned that the 2-(phenylthiomethyl)indoles might also be useful building blocks in organic synthesis.

In summary, we have developed a facile and efficient cyclization of 2-alkynylanilines for the synthesis of indole derivatives. As a result of the metal-free process, the ready availability of the starting materials



3 R = PhO, O-analogue of **1a**
4 R = *n*-C_5H_{11}, C-analogue of **1l**

Scheme 1. The O- and C-analogues.



Scheme 2.

Table 2. Synthesis of indole derivatives.[a]

$$\mathbf{1} \xrightarrow[\text{toluene, 90 °C}]{\text{0.1 equiv. DBU}} \mathbf{2}$$

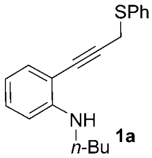
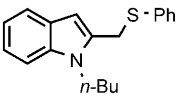
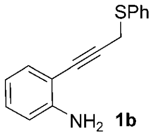
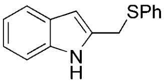
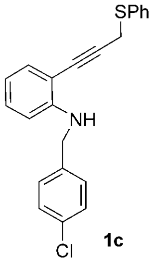
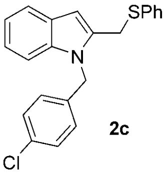
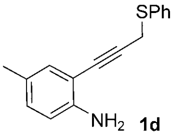
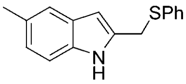
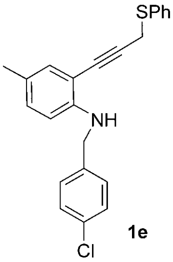
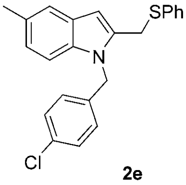
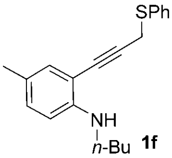
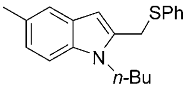
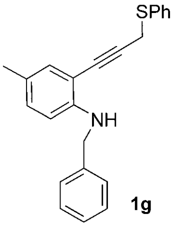
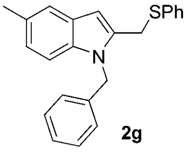
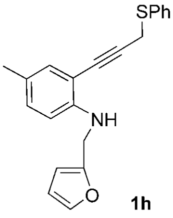
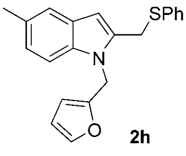
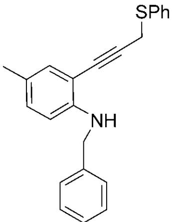
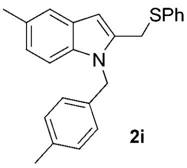
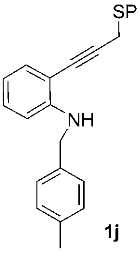
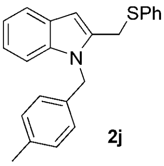
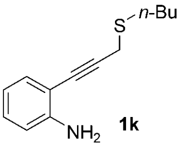
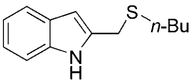
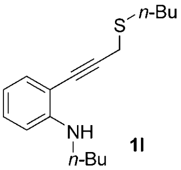
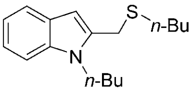
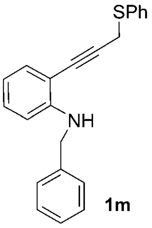
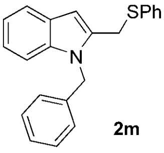
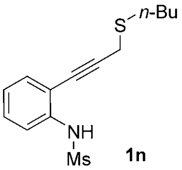
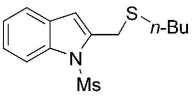
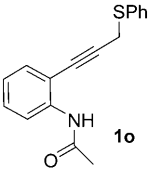
Entry	1	2	Yield [%]
1	 **1a**	 **2a**	84
2	 **1b**	 **2b**	82
3	 **1c**	 **2c**	88
4	 **1d**	 **2d**	72
5	 **1e**	 **2e**	86
6	 **1f**	 **2f**	80
7	 **1g**	 **2g**	89
8	 **1h**	 **2h**	85

Table 2. (Continued)

Entry	1	2	Yield [%]
9	 **1i**	 **2i**	83
10	 **1j**	 **2j**	86
11	 **1k**	 **2k**	82
12	 **1l**	 **2l**	66
13	 **1m**	 **2m**	88
14	 **1n**	 **2n**	54[b,c]
15	 **1o**	**2b**	79[b]

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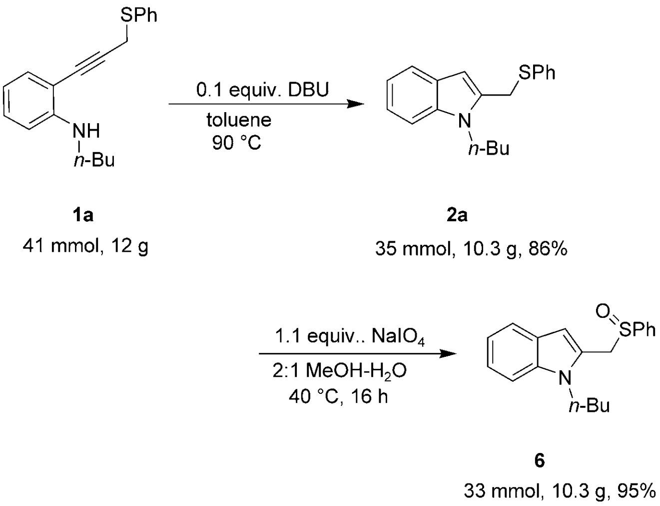
[a] All reactions were run under the following conditions, unless otherwise specified: 0.5 mmol of **1** and 0.05 mmol of DBU in 1 mL of toluene at 90 °C under an N_2 atmosphere for 30 h.

[b] 0.6 mmol of DBU was added.

[c] 36% of **2k** was observed.



1a
41 mmol, 12 g

2a
35 mmol, 10.3 g, 86%

6
33 mmol, 10.3 g, 95%

Scheme 3.

and the simple and convenient operation, the type of reaction presented here has potential utility in organic synthesis. A 10-gram scale preparation may demonstrate the possibility of the application in the environmentally friendly synthesis of indole derivatives.

Experimental Section

General Procedure for the Synthesis of 2a

To 0.5 mmol of *N*-butyl-2-[3-(phenylthio)prop-1-ynyl]aniline (**1a**) was added 1 mL of DBU in toluene (0.05 M) under an N_2 atmosphere, followed by a heating to 90 °C for 30 h. After evaporation, chromatography on silica gel (eluent: EtOAc/petroleum ether = 1:20) of the reaction mixture afforded the desired product **2a** as an oil; yield: 124 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53–7.51$ (d, $J = 7.6$ Hz, 1H), 7.35–7.33 (d, $J = 7.2$ Hz, 2H), 7.31–7.24 (m, 3H), 7.21–7.16 (m, 2H), 7.09–7.06 (t, $J = 7.4$ Hz, 1H), 6.32 (s, 1H), 4.24 (s, 2H), 4.17–4.13 (t, $J = 7.6$ Hz, 2H), 1.83–1.75 (m, 2H), 1.43–1.33 (m, 2H), 0.97–0.93(t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 137.2$, 135.7, 134.6, 130.7, 129.0, 127.5, 126.9, 121.4, 120.5, 119.4, 109.5, 102.4, 43.4, 32.4, 31.5, 20.5, 13.9; MS: $m/z = 295$ (M, 22), 109 (PhS, 100); IR (neat): $\nu = 1583.8$, 1480.9 cm^{-1}; HR-MS: $m/z = 295.1389$, calcd for $C_{19}H_{21}NS$: 295.1395.

Acknowledgements

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[6] The substrates (**1a–1o**) could be easily prepared *via* a Sonogashira reaction. **Typical Procedure for the Synthesis of 1a:** To a solution of *N*-butyl-2-iodoaniline (2.0 mmol) and phenyl(prop-2-ynyl)sulfane (2.2 mmol) in 10 mL of THF was added CuI (10 mg. 0.05 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), then 1 mL of Et_3N was added under an N_2 atmosphere at room temperature for 2 h. The reaction mixture was quenched with water, extracted with Et_2O, and dried over anhydrous Na_2SO_4. After evaporation of the Et_2O, chromatography on silica gel (eluent: EtOAc/petroleum ether = 1:15) of the crude product afforded **1a** in a yield of 92%.

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