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A new synthesis of indoles via intramolecular cyclization of *o*-alkynyl *N,N*-dialkylanilines promoted by KO*t*-Bu/DMSO

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ABSTRACT

2-Aryl indoles could be prepared in excellent yields via the intramolecular cyclization of *o*-alkynyl *N,N*-dialkylanilines. The reaction is efficiently promoted by the catalytic amount of KO*t*-Bu in DMSO at room temperature. A reaction mechanism involving α-aminoalkyl radical intermediates is suggested.

Indole derivatives possess a variety of interesting biological activities.[1] They are also the privileged structure motif of many natural products. The synthetic methods of indole derivatives have been extensively studied.[2] The classical methods include Fischer indole synthesis, Larock heteroannulation, and reductive cyclization. In recent years, new approaches via the direct functionalizations of C—H bonds of amides, enamines, and acylhydrazines have also been developed.[3] Patel and Liang reported the synthesis of 3-aryl indoles via transition-metal catalyzed oxidative coupling of *o*-alkynyl *N,N*-dialkyl anilines.[4,5] Zhou and co-workers reported visible-light promoted radical addition of *o*-alkynyl *N,N*-dialkylanilines. A series of indoles were prepared in good yields.[6] Recently, we reported the new synthesis of indole derivatives via the intramolecular coupling of tertiary amines and ketones in the presence of KO*t*-Bu/DMF.[7] We also found that KO*t*-Bu/DMF can promote the intramolecular cyclization of *o*-alkenyl *N,N*-dialkyl anilines.[8] In these transformations, the generation of α-aminoalkyl radicals is proposed based on a series of experiment evidences. We speculated that the intramolecular trapping of α-aminoalkyl radicals with alkynes can provide a new approach for the synthesis of nitrogen heterocycles. In this Letter, we report the intramolecular cyclization of *o*-alkynyl *N,N*-dialkylanilines promoted by KO*t*-Bu/DMSO. The reaction provided 2-aryl indoles in excellent yields.

Initially, the reaction of **1a** was examined in DMF with 1.5 equiv of KO*t*-Bu at 90 °C. To our delight, the expected indole product **2a** was obtained in an excellent yield (Table 1, entry 1). The reaction conditions were optimized and the results are summarized in Table 1. The reaction also occurred at room temperature, but a lower yield was obtained (Table 1, entry 2). The effect of reaction solvents was also examined (Table 1, entries 3–7). DMSO was found to be a better solvent than DMF. An excellent yield (95%) could be obtained in DMSO at room temperature (Table 1, entry 3). Other solvents such as CH_2Cl_2, THF, toluene, and CH_3CN are incompatible with the reaction (Table 1, entries 4–7). The replacement of KO*t*-Bu with KOMe led to a lower yield (Table 1, entry 8). The application of other bases such as NaOMe, KOH, and K_2CO_3 did not give product **2a** (Table 1, entries 9–11). The effect of KO*t*-Bu loading was also examined (Table 1, entries 12 and 13). Excellent yields were kept with 0.3 and 0.1 equiv of KO*t*-Bu. The further decrease of the KO*t*-Bu loading (0.05 equiv) resulted in a loss of the yield.

With the optimal reaction conditions in hand, a range of *N,N*-disubstituted-2-(phenylethynyl)anilines were examined and the results are summarized in Table 2. The substrates **1b, 1d**–**1h** with electron-withdrawing groups including 2-chloro, 3-chloro, 4-fluoro, 4-chloro, 4-trifluoromethyl, 4-cyano provided the indoles **2b**, **2d**–**2h** in good yields (Table 2, entries 2, 4–8). The introduction of 2-methoxy, 4-methoxy groups is also tolerable, however 1.5 equiv of KO*t*-Bu were required to achieve excellent yields (Table 2, entries 3 and 9). The reaction of *N*-naphthyl and *N*-quinolinyl substrates **1j**–**1k** provided the products in excellent yields (Table 2, entries 10 and 11). *N,N*-Dibenzyl substrate **1l** is also applicable. Product **2l** was obtained in a good yield (Table 2, entry 12).

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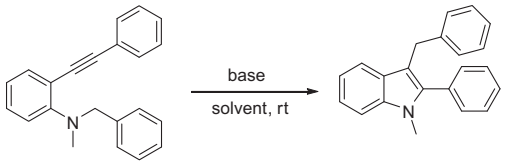
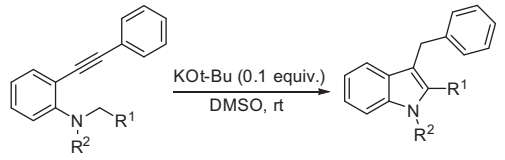
Table 1
Intramolecular cyclization of **1a**[a]



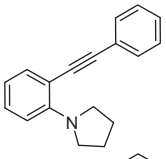
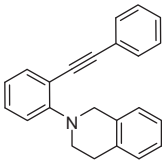
Entry	Solvent	Base (equiv)	Yield[b]/%
1[c]	DMF	KO*t*-Bu (1.5)	96
2	DMF	KO*t*-Bu (1.5)	83
3	DMSO	KO*t*-Bu (1.5)	95
4	CH_2Cl_2	KO*t*-Bu (1.5)	0
5	THF	KO*t*-Bu (1.5)	0
6	Toluene	KO*t*-Bu (1.5)	0
7	CH_3CN	KO*t*-Bu (1.5)	0
8	DMSO	KOMe (1.5)	71
9	DMSO	NaOMe (1.5)	0
10	DMSO	KOH (1.5)	0
11	DMSO	K_2CO_3 (1.5)	0
12	DMSO	KO*t*-Bu (0.3)	93
13	DMSO	KO*t*-Bu (0.1)	94

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), base, solvent (1.5 mL), at rt, under an argon atmosphere, 1 h.
[b] Isolated yields.
[c] Reaction was carried out at 90 °C.

Table 2
Intramolecular cyclization of substrates **1a-1o**[a]

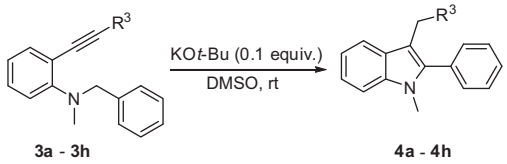


1a - 1o **2a - 2o**

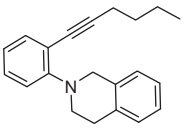
Entry	R^1	R^2	Product	Yield[b]/%
1	Ph	Me	**2a**	94
2	2-Cl-C_6H_4	Me	**2b**	91
3[c]	2-MeO-C_6H_4	Me	**2c**	90
4	3-Cl-C_6H_4	Me	**2d**	92
5	4-F-C_6H_4	Me	**2e**	95
6	4-Cl-C_6H_4	Me	**2f**	88
7	4-CF_3-C_6H_4	Me	**2g**	91
8	4-CN-C_6H_4	Me	**2h**	86
9[c]	4-MeO-C_6H_4	Me	**2i**	92
10	2-Naphthyl	Me	**2j**	95
11	2-Quinolinyl	Me	**2k**	94
12	Ph	benzyl	**2l**	88
13	H	Me	**2m**	0
14			**2n**	0
15[d]			**2o**	77

[a] Reaction conditions: **1a**–**1o** (0.2 mmol, 1.0 equiv), KO*t*-Bu (0.02 mmol, 0.1 equiv), DMSO (1.5 mL), argon atmosphere, rt, 1 h.
[b] Isolated yields.
[c] KO*t*-Bu (0.3 mmol, 1.5 equiv) was used.
[d] KO*t*-Bu (0.1 mmol, 0.5 equiv) was used.

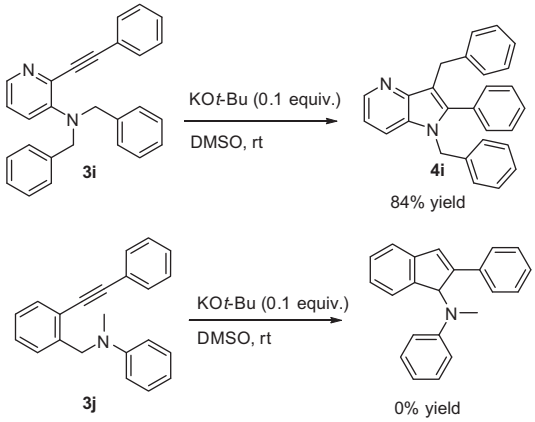
Table 3
Intramolecular cyclization of 2-(phenylethynyl)aniline derivatives[a]



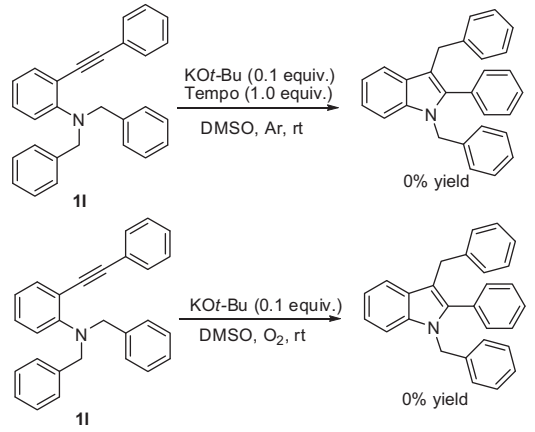
3a - 3h **4a - 4h**

Entry	R^3	Product	Yield[b]/%
1	4-F-C_6H_4	**4a**	93
2	4-Cl-C_6H_4	**4b**	89
3	4-MeO-C_6H_4	**4c**	89
4	4-CF_3-C_6H_4	**4d**	0
5	1-Naphthyl	**4e**	90
6	H	**4f**	66
7[c]	*n*-Butyl	**4g**	54
8[d]		**4h**	37

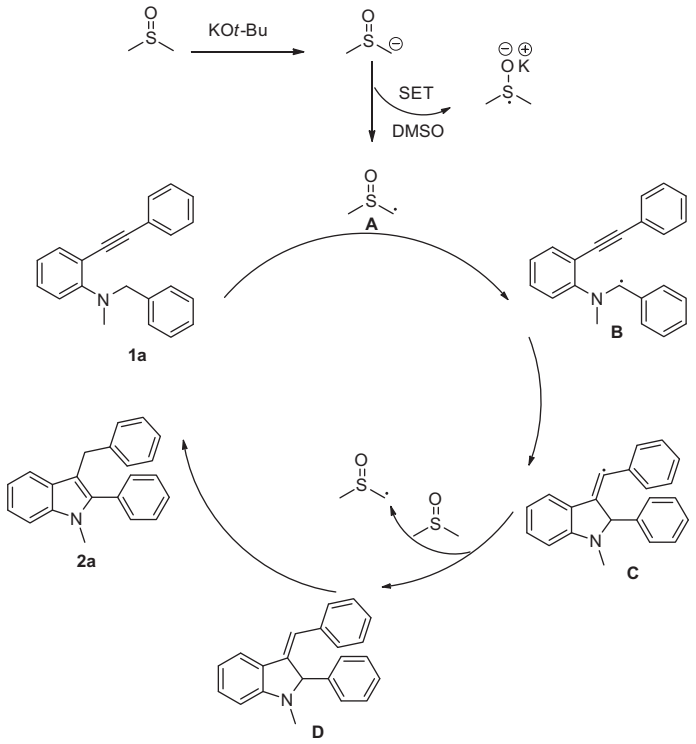
[a] Reaction conditions: **3a**-**3h** (0.2 mmol, 1.0 equiv), KO*t*-Bu (0.02 mmol, 0.1 equiv), DMSO (1.5 mL), argon atmosphere, rt, 1 h.
[b] Isolated yields.
[c] KO*t*-Bu (0.04 mmol, 0.2 equiv) was used.
[d] KO*t*-Bu (0.1 mmol, 0.5 equiv) was used.



Scheme 1. Intramolecular cyclization of **3i** and **3j**.



Scheme 2. Free radical inhibition experiments with Tempo and oxygen.



Scheme 3. Tentative reaction mechanism.

N,*N*-Dimethyl and pyrrolidinyl substrates (**1m**–**1n**) did not provide the expected products (Table 2, entries 13 and 14). The activation effect of α-aryl groups seems to be necessary for the reaction. Tetrahydroisoquinoline derived substrate **1o** provided product **2o** in a moderate yield (Table 2, entry 15).

Furthermore, we examined the influence of the substitution of the alkyne moiety. The results are summarized in Table 3. The substitution of benzene ring with 4-fluoro, 4-chloro, and 4-methoxyl group did not affect the yield substantially (Table 3, entries 1–3). However, the substitution with trifluoromethyl group completely inhibited the reaction (Table 3, entry 4). The similar results were also observed in the reactions promoted by KO*t*-Bu/DMF.[7,8] The exact reason still remains elusive. When naphthyl alkyne **3e** was examined, a good yield was obtained (Table 3, entry 5). The terminal alkyne **3f** is also applicable, however only a moderate yield was obtained (Table 3, entry 6). Butyl alkyne **3g** gave a lower yield (Table 3, entry 7). The reaction of tetrahydroisoquinoline derived alkyne **3h** provided the expected product **4h** in a low yield (Table 3, entry 8). In this case, higher KO*t*-Bu loading (0.5 equiv) was required.

We prepared the substrate **3i** with pyridine backbone. The reaction of **3i** occurred smoothly and gave the product **4i** in a good yield (Scheme 1). *N*-Methyl-*N*-(2-(phenylethynyl)benzyl)aniline **3j** was also examined, but no reaction was observed (Scheme 1).

To probe the reaction mechanism, two controlling experiments were carried out. The reaction was found to be inhibited completely in the presence of Tempo (2,2,6,6-tetramethyl-piperidine-1-oxyl) or oxygen (Scheme 2). Based on the results and our previous studies, a reaction mechanism is proposed in Scheme 3.[8] DMSO is deprotonated to give an anion. The anion transfers an electron to another DMSO molecule and a DMSO radical **A** is generated.[9] **A** abstracts a hydrogen from the substrate **1a** to give α-amino alkyl radical **B**. Following an intramolecular radical cyclization, the intermediate **C** is generated. After the abstraction of a hydrogen atom from DMSO, the primary product **D** is formed.[10] **D** undergoes an allyl rearrangement to give product **2a**.[11]

In conclusion, we have developed a new intramolecular cyclization of *o*-alkynyl *N*,*N*-dialkylanilines. The reaction can be efficiently promoted by the combination of KO*t*-Bu and DMSO. A number of 2-aryl indoles were prepared in good yields. A reaction mechanism via the α-aminoalkyl radical intermediate is suggested. The DMSO radical generated in KO*t*-Bu/DMSO system probably works as the crucial initiator. The reaction provides a practical synthesis of 2-aryl indoles from readily available 2-amino-phenylacetylene derivatives.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.002.

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10. One reviewer suggested that the radical **C** abstracts a hydrogen atom from **1a** to regenerate **B**. Thus a typical radical chain reaction is initiated. These two reaction pathways cannot be distinguished from the present experiment evidences.
11. Although the reaction mechanism via the α-amino alkyl anions cannot be excluded, the accumulated experiment evidences from a series of reactions promoted by KO*t*-Bu/DMF and KO*t*-Bu/DMSO are more favorable with the α-amino alkyl radical mechanism. See Refs. 7,8 for the details.