Tetrahedron 67 (2011) 1178–1182

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot synthesis of substituted indolines via a copper-catalyzed sequential multicomponent/C–N coupling reaction

Hongwei Jin [a,b], Bingwei Zhou [b], Zhi Wu [b], Yang Shen [a], Yanguang Wang [a,*]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China
[b] College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, PR China

ARTICLE INFO

Article history:
Received 5 October 2010
Received in revised form 20 November 2010
Accepted 30 November 2010
Available online 4 December 2010

Keywords:
Indolines
Copper
Multicomponent reactions
C–N coupling
Cascade reactions

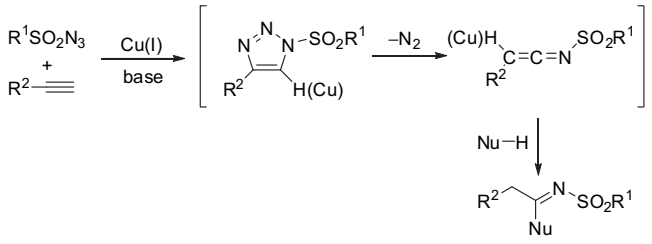
ABSTRACT

One-pot synthesis of 2-(*N*-sulfonylimino)indolines has been developed. The procedure combines the copper-catalyzed three-component reaction of sulfonyl azides, *o*-bromophenylacetylenes, and amines and the copper-catalyzed intramolecular C–N coupling in one sequence, which afforded the products in moderate to good yields. The resulting 2-(*N*-sulfonylimino)indolines could be easily transformed to pharmaceutically valuable oxindoles (indolin-2-ones).

1. Introduction

In the field of organic synthesis, it would be desirable to perform a series of simple steps in one pot,[1] which would minimize the chemicals used and waste produced, as well as the reaction time consumed. As a result, great attention has been paid to the development of cascade reaction. Multicomponent reactions (MCRs) involving a cascade process with at least three different substrates to generate complex molecular frameworks have emerged as a powerful synthetic strategy.[2]

Indoline and its derivatives are highly important scaffolds found in numerous biologically active natural products.[3] Consequently, a great number of methods have been developed for construction of this important class of compounds.[4] MCRs approach to indulines rings is rare. Ketenimine,[5] as a useful intermediate, has attracted much attention due to its easy formation, relative reactivity, and diverse chemistry.[6] The most attractive and sustainable method generating ketenimines could be attributed to the copper-catalyzed azide-alkyne cycloaddition (CuAAC) (Scheme 1), which was established by Fokin et al.[7] This method is suitable for MCRs. Chang,[8] our group[9] and others[10] developed a number of three- or four-component reactions by trapping ketenimines generated in situ from sulfonyl azides and terminal alkynes via this CuAAC process. Herein, we report our results on the copper-catalyzed three-component cascade reaction of sulfonyl azides, 2-bromophenylacetylenes and amines, which furnished 2-sulfonyliminoindolines in moderate to good yields.



Scheme 1. Formation of ketenimine via a the copper-catalyzed azide-alkyne cycloaddition (CuAAC).

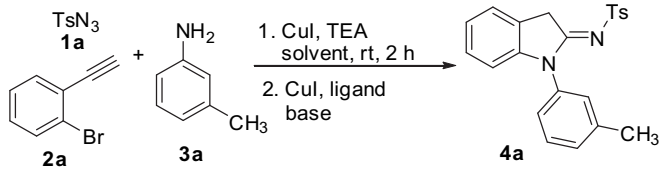
2. Results and discussion

In our primary investigations, we selected the CuI-catalyzed reaction of *p*-toluenesulfonyl azide (**1a**), *o*-bromophenyl-acetylene (**2a**), and *m*-toluidine (**3a**) as the model reaction (Table 1). In order to optimize the reaction conditions, several ligands, and bases were examined. When the reaction was conducted firstly in the presence of 0.1 equiv of CuI and 1 equiv of triethylamine (TEA) in DMSO at room temperature for 2 h, and then under 0.1 equiv of CuI, 0.4 equiv of *N*-methylglycine[11] and 2.0 equiv of K_2CO_3 at room temperature for 4 h,

* Corresponding author. Tel.: +86 571 87951512; e-mail address: orgwyg@zju.edu.cn (Y. Wang).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.094

Table 1
Optimization of reaction conditions[a]



Entry	Solvent	Ligand[b]	Base	Temp[c] (°C)	Yield[d] (%)
1	DMSO	A	K_2CO_3	rt	0
2	DMSO	A	K_2CO_3	60	35
3	DMSO	B	K_2CO_3	60	46
4	DMSO	C	K_2CO_3	60	60
5	DMSO	D	K_2CO_3	60	32
6	DMSO	E	K_2CO_3	60	25
7	DMSO	F	K_2CO_3	60	20
8	DMSO	C	K_3PO_4	60	50
9	DMSO	C	Cs_2CO_3	60	55
10	DMF	C	K_2CO_3	60	53
11	DMSO	C	K_2CO_3	80	55[e]

[a] Reaction conditions: *p*-toluenesulfonyl azide (0.6 mmol), *o*-bromophenylacetylene (0.5 mmol), *m*-toluidine (0.55 mmol), TEA (0.5 mmol), CuI (0.05 mmol), solvent (2 mL), rt, 2 h, then CuI (0.05 mmol), ligand (0.2 mmol), base (1 mmol), 4 h.
[b] Ligand: A=*N*-methylglycine; B=*N*,*N*-dimethylglycine; C=L-proline; D=*N*,*N*-dimethylethane-1,2-diamine; E=1,10-phenanthroline; F=ethyl 2-oxocyclo-hexanecarboxylate.
[c] Reaction temperature refer to the intramolecular C–N coupling.
[d] Isolated yield for **4a** refer to **2a**.
[e] Intramolecular coupling reaction time: 8 h.

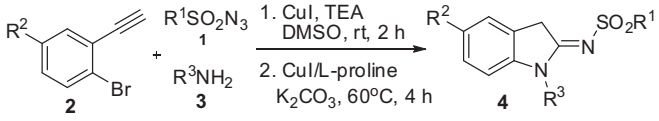
we did not obtained the desired product **4a** (Table 1, entry 1). However, when the intramolecular C–N coupling reaction temperature was increased to 60 °C, **4a** was yielded in 35% yield (Table 1, entry 2). When we turned our attention to screen conditions of the C–N coupling step with five representative ligands, i.e., *N*,*N*-dimethylglycine, L-proline[12] (Table 1, entries 3–4), *N*,*N*-dimethylethane-1,2-diamine[13] (Table 1, entry 5), 1,10-phenanthroline[14] (Table 1, entry 6), and ethyl 2-oxocyclohexanecarboxylate[15] (Table 1, entry 7), L-proline was found to be the best ligand for this intramolecular C–N coupling. When K_3PO_4 (Table 1, entry 8) or Cs_2CO_3 (Table 1, entry 9) was used as the base, no further improvement in yield was achieved. Changing the solvent DMSO to DMF also did not enhance the yield of **4a** (Table 1, entry 10). Prolonging the reaction time could not improve the result (Table 1, entry 11).

The optimized reaction conditions for the formation of **4a** were applied to a wide range of substrates. As shown in Table 2, both aromatic (Table 2, entries 1–6 and 11–21) and aliphatic sulfonyl azides (Table 2, entries 7–10) could work to afford the desired products. The strong electron-withdrawing group substituted aromatic amines, such as 3-nitroaniline (**3g**) (Table 2, entry 16) and 4-nitroanline (**3h**) (Table 2, entry 17), gave much lower yields than other aromatic amines (Table 2, entries 1–15, 20, and 21). We also examined benzyl (Table 2, entry 18) and aliphatic amines (Table 2, entry 19), but they gave the desired products in poor yields and required higher reaction temperature (80 °C) and stronger base for the intramolecular C–N coupling.

A plausible mechanism for this cascade process was outlined in Scheme 2. In the presence of TEA and CuI, *p*-tolylsulfonyl azide (**1a**) reacts with *o*-bromophenylacetylene (**2a**) to form the ketenimine species **A**.[7] **A** is quickly attacked by nucleophile **3a** to generate *N*-sulfonylamidine **B**, which easily tautomerize to more stable sulfonamide **C**. The subsequent CuI/L-proline catalyzed intramolecular C–N coupling of **C** affords the desired product **4a**.

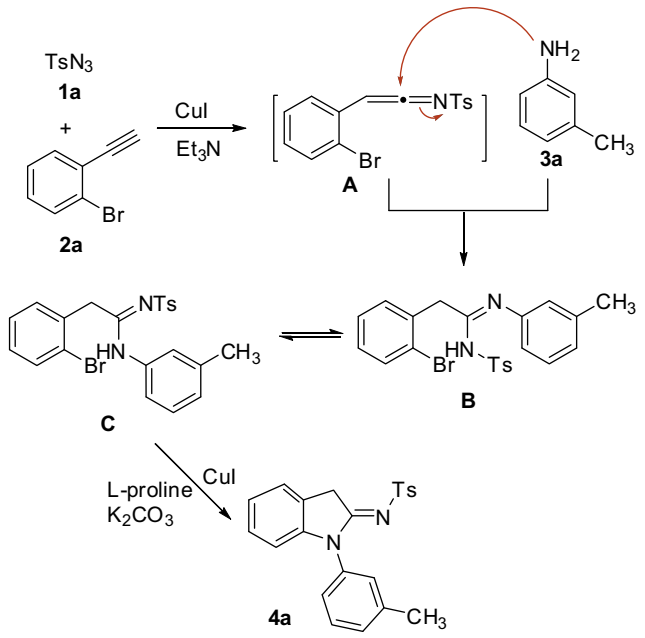
As next step, we investigated the synthetic application of this method by hydrolysis of the resulting **4a**. Thus, **4a** was treated with concentrated hydrochloric acid under reflux condition to afford oxindole (indolin-2-one) **5a** (Scheme 3), which constitute a pharmaceutically valuable class of biologically active compounds.[16,17]

Table 2
One-pot synthesis of 2-sulfonyliminoindolines **4**[a]

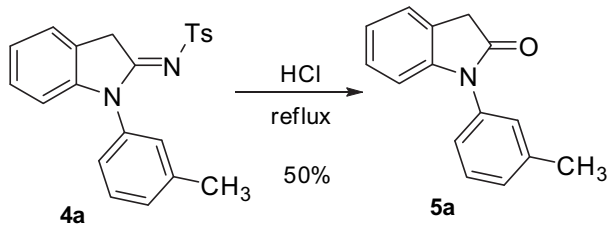


Entry	**1** (R^1)	**2** (R^2)	**3** (R^3)	Yield[b] (%)
1	**1a**(4-MeC_6H_4)	**2a** (H)	**3a** (3-MeC_6H_4)	60 (**4a**)
2	**1b** (2-MeC_6H_4)	**2a**	**3a**	45 (**4b**)
3	**1c** (C_6H_5)	**2a**	**3a**	40 (**4c**)
4	**1d** (4-ClC_6H_4)	**2a**	**3a**	51 (**4d**)
5	**1e** (4-*i*-PrC_6H_4)	**2a**	**3a**	61 (**4e**)
6	**1f** (4-$MeOC_6H_4$)	**2a**	**3a**	55 (**4f**)
7	**1g** (*n*-Bu)	**2a**	**3a**	72 (**4g**)
8	**1h** (Me)	**2a**	**3a**	62 (**4h**)
9	**1g**	**2a**	**3b** (4-ClC_6H_4)	70 (**4i**)
10	**1h**	**2a**	**3b**	43 (**4j**)
11	**1a**	**2a**	**3c**(4-$MeOC_6H_4$)	45 (**4k**)
12	**1a**	**2a**	**3d** (3,5-$Me_2C_6H_3$)	65 (**4l**)
13	**1a**	**2a**	**3e** (C_6H_5)	56 (**4m**)
14	**1a**	**2a**	**3f**(3-ClC_6H_4)	45 (**4n**)
15	**1a**	**2a**	**3b**	60 (**4o**)
16	**1a**	**2a**	**3g**(3-$NO_2C_6H_4$)	36 (**4p**)
17	**1a**	**2a**	**3h** (4-$NO_2C_6H_4$)	26 (**4q**)
18	**1a**	**2a**	**3i** ($C_6H_5CH_2$)	25 (**4r**)[c]
19	**1a**	**2a**	**3j** (*i*-Pr)	17 (**4s**)[c]
20	**1a**	**2b** (MeO)	**3a**	50 (**4t**)
21	**1a**	**2c**(Cl)	**3a**	43 (**4u**)

[a] Reaction conditions: sulfonyl azides (0.6 mmol), *o*-bromophenylacetylenes (0.5 mmol), amines (0.55 mmol), TEA (0.5 mmol), CuI (0.05 mmol), DMSO (2 mL), rt, 2 h, then CuI (0.05 mmol), L-proline (0.2 mmol), K_2CO_3 (1 mmol), 60 °C, 4 h.
[b] Isolated yields for **4** refer to *o*-bromophenylacetylenes.
[c] For the intramolecular coupling: Cs_2CO_3 (1 mmol), 80 °C.



Scheme 2. Possible mechanism for the formation of **4a**.



Scheme 3. Transformation of **4a**.

3. Conclusion

In conclusion, we have developed a novel synthesis of 2-(*N*-sulfonylimino)-indolines via a copper-catalyzed three-component of sulfonyl azides, terminal alkynes, and amines. This one-pot approach is mild and general, and the substrates are readily available. The resulting product could be easily transformed to pharmaceutically valuable oxindoles. Further synthetic applications for this method are under investigation in our laboratory.

4. Experimental

4.1. General procedure for the copper-catalyzed one-pot synthesis of 2-sulfonyliminoindolines 4

To a solution of sulfonyl azides **1** (0.6 mmol), *o*-bromo-phenylacetylenes **2** (0.5 mmol), aromatic amines **3** (0.55 mmol), and CuI (0.05 mmol) in DMSO (2 mL) in Schlenk tube was added TEA (0.5 mmol) slowly via a syringe. The reaction solution was stirred at room temperature under N_2 for 2 h. The solution was then added to CuI (0.05 mmol), K_2CO_3 (1 mmol), and L-proline (0.2 mmol), and the mixture was stirred at 60 °C under N_2 for 4 h. The reaction mixture was partitioned between ethyl acetate and saturated aq NH_4Cl, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate (6:1 to 9:1).

*4.1.1. 1-(m-Tolyl)-2-(p-toluenesulfonylimino)indoline (**4a**).* White solid; mp 131–132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, J=8.5 Hz, 2H), 7.38 (q, J=7.5 Hz, 2H), 7.26–7.23 (m, 4H), 7.14–7.12 (m, 3H), 6.75 (d, J=8.0 Hz, 1H), 4.41 (s, 2H), 2.40 (s, 3H), 2.39 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 144.7, 142.6, 139.7, 139.4, 134.3, 129.7, 129.4, 129.2, 127.9, 127.6, 126.6, 126.1, 124.5, 124.1, 123.8, 110.5, 36.4, 21.5, 21.4; EIMS m/z 376 (M^+); HRMS (EI) calcd for $C_{22}H_{20}N_2O_2S$ ($[M]^+$), 376.1245; found, 376.1265.

*4.1.2. 1-(m-Tolyl)-2-(o-toluenesulfonylimino)indoline (**4b**).* White solid; mp 155–156 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (q, J=8.0 Hz, 1H), 7.40–7.36 (m, 3H), 7.28–7.19 (m, 4H), 7.14–7.10 (m, 3H), 6.73 (d, J=8.0 Hz, 1H), 4.41 (s, 2H), 2.56 (s, 3H), 2.39 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 144.7, 140.1, 139.7, 137.7, 134.3, 132.2, 129.7, 129.4, 127.9, 127.8, 127.7, 126.1, 125.5, 124.5, 124.1, 123.8, 110.5, 36.6, 21.3, 20.3; EIMS m/z 376 (M^+); HRMS (EI) calcd for $C_{22}H_{20}N_2O_2S$ ($[M]^+$), 376.1245; found, 376.1257.

*4.1.3. 1-(m-Tolyl)-2-(benzenesulfonylimino)indoline (**4c**).* White solid; mp 128–129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (t, J=8.5 Hz, 2H), 7.52–7.38 (m, 5H), 7.26–7.20 (m, 1H), 7.15–7.12 (m, 3H), 6.76 (d, J=8.0 Hz, 1H), 4.43 (s, 2H), 2.40(s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 144.7, 142.3, 139.7, 134.2, 132.0, 129.7, 129.4, 128.6, 128.0, 127.6, 126.5, 126.1, 124.6, 124.0, 123.9, 110.6, 36.5, 21.4; EIMS m/z 362 (M^+); HRMS (EI) calcd for $C_{21}H_{18}N_2O_2S$ ($[M]^+$), 362.1089; found, 362.1106.

*4.1.4. 1-(m-Tolyl)-2-(p-chlorobenzenesulfonylimino)indoline (**4d**).* White solid; mp 153–154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (q, J=7.0 Hz, 2H), 7.42–7.38 (m, 4H), 7.26–7.22 (m, 2H), 7.16–7.13 (m, 3H), 6.76 (d, J=8.0 Hz, 1H), 4.43 (s, 2H), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 144.6, 140.9, 139.8, 138.3, 134.1, 129.8, 129.5, 128.9, 128.0, 127.5, 126.0, 124.6, 124.1, 124.0, 110.6, 36.6, 21.4; EIMS m/z 396 (M^+); HRMS (EI) calcd for $C_{21}H_{17}ClN_2O_2S$ ($[M]^+$), 396.0699; found, 396.0720.

*4.1.5. 1-(m-Tolyl)-2-(p-isopropylbenzenesulfonylimino)indoline (**4e**).* White solid; mp 118–119 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (d, J=8.5 Hz, 2H), 7.40–7.36 (m, 2H), 7.31–7.19 (m, 4H), 7.15–7.12 (m, 3H), 6.75 (d, J=8.0 Hz, 1H), 4.41 (s, 2H), 2.97–2.91 (m, 1H), 2.40 (s, 1H), 1.25 (s, 3H), 1.24 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 153.4, 144.7, 139.7, 139.6, 134.3, 129.7, 129.4, 127.9, 127.6, 126.7, 126.6, 126.1, 124.5, 124.1, 123.8, 110.5, 36.4, 34.1, 23.7, 21.3; EIMS m/z 404 (M^+); HRMS (EI) calcd for $C_{24}H_{24}N_2O_2S$ ($[M]^+$), 404.1559; found, 404.1577.

*4.1.6. 1-(m-Tolyl)-2-(p-methoxybenzenesulfonylimino)indoline (**4f**).* White solid; mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (d, J=9.0 Hz, 2H), 7.40–7.36 (m, 2H), 7.26–7.19 (m, 2H), 7.14–7.12 (m, 3H), 6.92 (d, J=9.0 Hz, 2H), 6.74 (d, J=7.5 Hz, 1H), 4.40 (s, 2H), 3.83 (s, 3H), 2.39 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 162.4, 144.7, 139.7, 134.3, 134.2, 129.7, 129.5, 128.6, 127.9, 127.6, 126.1, 124.6, 124.1, 123.8, 113.8, 110.5, 55.6, 36.4, 21.4; EIMS m/z 392 (M^+); HRMS (EI) calcd for $C_{22}H_{20}N_2O_3S$ ($[M]^+$), 392.1195; found, 392.1234.

*4.1.7. 1-(m-Tolyl)-2-(butanesulfonylimino)indoline (**4g**).* White solid; mp 74–75 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44–7.36 (m, 2H), 7.28–7.26 (m, 1H), 7.24–7.11 (m, 4H), 6.76 (d, J=7.5 Hz, 1H), 4.44 (s, 2H), 3.03 (t, J=8.0 Hz, 2H), 2.43 (s, 3H), 1.81–1.74 (m, 2H), 1.43–1.35 (m, 2H), 0.89 (t, J=7.5 Hz, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 144.8, 139.7, 134.4, 129.6, 129.4, 127.8, 127.7, 126.1, 124.5, 124.1, 123.7, 110.3, 54.1, 36.4, 25.6, 21.4, 21.3, 13.6; EIMS m/z 342 (M^+); HRMS (EI) calcd for $C_{19}H_{22}N_2O_2S$ ($[M]^+$), 342.1402; found, 342.1420.

*4.1.8. 1-(m-Tolyl)-2-(methanesulfonylimino)indoline (**4h**).* White solid; mp 97–98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45–7.41 (m, 1H), 7.39–7.37 (m, 1H), 7.29–7.26 (m, 1H), 7.22–7.17 (m, 3H), 7.15–7.12 (m, 1H), 6.73 (d, J=8.0 Hz, 1H), 4.44 (s, 2H), 2.99 (s, 3H), 2.43 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 144.8, 139.8, 134.3, 129.7, 129.5, 127.9,

127.7, 126.1, 124.5, 124.2, 123.8, 110.4, 42.5, 36.4, 21.4; EIMS *m/z* 300 (M^+); HRMS (EI) calcd for $C_{16}H_{16}N_2O_2S$ ($[M]^+$), 300.0932; found, 300.0945.

*4.1.9. 1-(p-Chlorophenyl)-2-(butanesulfonylimino)indoline (**4i**).* White solid; mp 126–127 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.54–7.51 (m, 2H), 7.38 (d, *J*=7.5 Hz, 1H), 7.36–7.34 (m, 2H), 7.27–7.21 (m, 1H), 7.16–7.14 (m, 1H), 6.75 (d, *J*=7.5 Hz, 1H), 4.44 (s, 2H), 3.03 (t, *J*=8.0 Hz, 2H), 1.80–1.73 (m, 2H), 1.44–1.36 (m, 2H), 0.90 (t, *J*=8.0 Hz, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 144.2, 134.6, 133.0, 129.9, 128.6, 128.0, 126.0, 124.7, 124.0, 110.0, 54.1, 36.3, 25.5, 21.4, 13.6; EIMS *m/z* 362 (M^+); HRMS (EI) calcd for $C_{18}H_{19}ClN_2O_2S$ ($[M]^+$), 362.0856; found, 362.0868.

*4.1.10. 1-(p-Chlorophenyl)-2-(methanesulfonylimino)indoline (**4j**).* White solid; mp 184–185 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55–7.51 (m, 2H), 7.40–7.34 (m, 3H), 7.27–7.22 (m, 1H), 7.17–7.13 (m, 1H), 6.75 (d, *J*=7.5 Hz, 1H), 4.44 (s, 2H), 3.00(s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 144.3, 134.7, 132.9, 130.1, 128.7, 128.1, 126.0, 124.8, 124.1, 110.1, 42.5, 36.3; EIMS *m/z* 320 (M^+); HRMS (EI) calcd for $C_{15}H_{13}ClN_2O_2S$ ($[M]^+$), 320.0386; found, 320.0402.

*4.1.11. 1-(p-Methoxyphenyl)-2-(p-toluenesulfonylimino)indoline (**4k**).* White solid; mp 184–185 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J*=8.0 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 1H), 7.27–7.19 (m, 5H), 7.14–7.12 (m, 1H), 7.01 (q, *J*=7.0 Hz, 2H), 6.73 (d, *J*=8.0 Hz, 1H), 4.40 (s, 2H), 3.86 (s, 3H), 2.39 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 159.7, 145.0, 142.7, 139.4, 129.3, 128.3, 128.0, 127.0, 126.6, 126.1, 124.6, 123.9, 115.0, 110.5, 55.6, 36.4, 21.5; EIMS *m/z* 392 (M^+); HRMS (EI) calcd for $C_{22}H_{20}N_2O_3S$ ($[M]^+$), 392.1195; found, 392.1209.

*4.1.12. 1-(3,5-Dimethylphenyl)-2-(p-toluenesulfonylimino)indoline (**4l**).* White solid; mp 158–159 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=7.5 Hz, 1H), 7.26–7.18 (m, 3H), 7.13–7.10 (m, 1H), 7.06 (s, 1H), 6.93 (s, 2H), 6.74 (d, *J*=8.0 Hz, 1H), 4.39 (s, 2H), 2.39 (s, 3H), 2.35 (s, 6H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 144.8, 142.6, 139.5, 139.4, 134.2, 130.6, 129.2, 127.9, 126.6, 124.6, 124.5, 123.8, 110.6, 36.4, 21.5, 21.3; EIMS *m/z* 390 (M^+); HRMS (EI) calcd for $C_{23}H_{22}N_2O_2S$ ($[M]^+$), 390.1402; found, 390.1416.

*4.1.13. 1-Phenyl-2-(p-toluenesulfonylimino)indoline (**4m**).* White solid; mp 160–161 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, *J*=8.0 Hz, 2H), 7.45–7.43 (m, 1H), 7.39–7.33 (m, 3H), 7.26–7.19 (m, 3H), 7.15–7.11 (m, 1H), 6.75 (d, *J*=8.0 Hz, 1H), 4.43 (s, 2H), 2.38 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 144.6, 142.6, 139.3, 134.4, 129.6, 129.2, 128.8, 127.9, 127.1, 126.5, 126.1, 124.6, 123.9, 110.4, 36.4, 21.5; EIMS *m/z* 362 (M^+); HRMS (ESI) calcd for $C_{21}H_{19}N_2O_2S$ ($[M+H]^+$), 363.1167; found, 363.1166.

*4.1.14. 1-(m-Chlorophenyl)-2-(p-toluenesulfonylimino)indoline (**4n**).* White solid; mp 118–119 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J*=8.0 Hz, 2H), 7.48–7.36 (m, 4H), 7.29–7.22 (m, 4H), 7.17–7.13 (m, 1H), 6.77 (d, *J*=8.0 Hz, 1H), 4.43 (s, 2H), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 144.0, 142.9, 139.1, 135.5, 135.2, 130.7, 129.4, 129.2, 128.1, 127.5, 126.6, 126.0, 125.5, 124.8, 124.2, 110.3, 36.4, 21.6; EIMS *m/z* 396 (M^+); HRMS (EI) calcd for $C_{21}H_{17}ClN_2O_2S$ ($[M]^+$), 396.0699; found, 396.0710.

*4.1.15. 1-(p-Chlorophenyl)-2-(p-toluenesulfonylimino)indoline (**4o**).* White solid; mp 185–186 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, *J*=8.0 Hz, 2H), 7.48 (q, *J*=6.5 Hz, 2H), 7.31–7.29 (m, 2H), 7.27–7.22 (m, 3H), 7.16–7.14 (m, 1H), 6.75 (d, *J*=8.0 Hz, 1H), 4.43 (s, 2H), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 144.1, 142.8, 139.0, 134.6, 132.8, 129.9, 129.3, 128.5, 128.0, 126.6, 126.0, 124.7, 124.1, 110.2, 36.3, 21.5; EIMS *m/z* 396 (M^+); HRMS (EI) calcd for $C_{21}H_{17}ClN_2O_2S$ ($[M]^+$), 396.0699; found, 396.0715.

*4.1.16. 1-(m-Nitrophenyl)-2-(p-toluenesulfonylimino)indoline (**4p**).* White solid; mp 151–152 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.31–8.28 (m, 2H), 7.80–7.70 (m, 4H), 7.43 (d, *J*=7.5 Hz, 1H), 7.29–7.24 (m, 3H), 7.21–7.17 (m, 1H), 6.79 (d, *J*=8.0 Hz, 1H), 4.48 (s, 2H), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 148.9, 143.3, 143.2, 138.7, 135.5, 133.2, 130.6, 129.4, 128.2, 126.6, 125.9, 125.0, 124.5, 123.6, 122.6, 109.9, 36.3, 21.5; EIMS *m/z* 407 (M^+); HRMS (EI) calcd for $C_{21}H_{17}N_3O_4S$ ($[M]^+$), 407.0940; found, 407.0977.

*4.1.17. 1-(p-Nitrophenyl)-2-(p-toluenesulfonylimino)indoline (**4q**).* White solid; mp 188–190 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.37 (q, *J*=7.0 Hz, 2H), 7.77 (d, *J*=8.5 Hz, 2H), 7.61 (q, *J*=7.0 Hz, 2H), 7.43 (d, *J*=7.5 Hz, 1H), 7.28–7.24 (m, 2H), 7.21–7.17 (m, 2H), 6.82 (d, *J*=8.0 Hz, 1H), 4.50 (s, 2H), 2.41 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.1, 147.2, 143.2, 140.0, 138.7, 130.0, 129.4, 128.2, 128.0, 126.6, 125.0, 124.9, 124.6, 110.0, 36.4, 21.5; EIMS *m/z* 407 (M^+); HRMS (ESI) calcd for $C_{21}H_{18}N_3O_4S$ ($[M+H]^+$), 408.1018; found, 408.1005.

*4.1.18. 1-Benzyl-2-(p-toluenesulfonylimino)indoline (**4r**).* White solid; mp 128–130 °C; ^1H NMR (CDCl3, 500 MHz) δ 7.85 (d, *J*=8.0 Hz, 2H), 7.32 (d, *J*=7.0 Hz, 1H), 7.28–7.19 (m, 8H), 7.10–7.06 (m, 1H), 6.89 (d, *J*=8.0 Hz, 1H), 5.07 (s, 2H), 4.30 (s, 2H), 2.41 (s, 3H), ^{13}C NMR (CDCl3, 125 MHz) δ 169.7, 143.1, 142.7, 139.4, 134.7, 129.3, 128.8, 128.0, 127.9, 126.6, 124.5, 123.7, 110.0, 45.7, 36.2, 21.5; EIMS *m/z* 376 (M^+); HRMS (ESI) calcd for $C_{22}H_{21}N_2O_2S$ ($[M+H]^+$), 377.1324; found, 377.1307.

*4.1.19. 1-iso-Propyl-2-(p-toluenesulfonylimino)indoline (**4s**).* White solid; mp 116–117 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (t, *J*=8.5 Hz, 2H), 7.33–7.25 (m, 4H), 7.15 (d, *J*=8.0 Hz, 1H), 7.11–7.07 (m, 1H), 5.00–4.97 (m, 1H), 4.18 (s, 2H), 2.41 (s, 3H), 1.48 (d, *J*=7.0 Hz, 6H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 142.6, 142.4, 139.6, 129.3, 127.7, 127.0, 126.6, 124.6, 123.2, 111.3, 67.1, 45.9, 36.2, 21.5, 18.9; EIMS *m/z* 328 (M^+); HRMS (ESI) calcd for $C_{18}H_{23}N_2O_2S$ ($[M+H]^+$), 329.1324; found, 329.1323.

*4.1.20. 1-(m-Tolyl)-2-(p-toluenesulfonylimino)-5-methoxyindo-line (**4t**).* White solid; mp 182–184 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J*=8.5 Hz, 2H), 7.38 (t, *J*=7.5 Hz, 1H), 7.26–7.21 (m, 3H), 7.14–7.11 (m, 2H), 6.96 (t, *J*=1.0 Hz, 1H), 6.74–6.71 (m, 1H), 6.66 (d, *J*=9.0 Hz, 1H), 4.37 (s, 2H), 3.79 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.1, 156.9, 142.5, 139.6, 139.5, 138.2, 134.4, 129.5, 129.3, 129.2, 127.4, 126.5, 123.9, 112.7, 111.2, 110.9, 55.8, 36.6, 21.4, 21.3; EIMS *m/z* 406 (M^+); HRMS (ESI) calcd for $C_{23}H_{23}N_2O_3S$ ($[M+H]^+$), 407.1429; found, 407.1427.

*4.1.21. -(m-Tolyl)-2-(p-toluenesulfonylimino)-5-chloroindoline (**4u**).* White solid; mp 152–154 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77 (d, *J*=8.5 Hz, 2H), 7.38 (t, *J*=8.0 Hz, 1H), 7.34 (s, 1H), 7.27–7.23 (m, 3H), 7.17 (q, *J*=8.5 Hz, 1H), 7.11–7.09 (m, 2H), 6.66 (d, *J*=8.5 Hz, 1H), 4.40 (s, 2H), 2.38 (s, 6H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.0, 143.2, 142.7, 139.8, 133.9, 129.8, 129.5, 129.2, 127.9, 127.7, 127.4, 126.5, 124.8, 123.9, 111.3, 36.2, 21.3; EIMS *m/z* 410 (M^+); HRMS (ESI) calcd for $C_{22}H_{20}ClN_2O_2S$ ($[M+H]^+$), 411.0934; found, 411.0931.

4.2. Procedure for transformation of 2-iminoindoline 4a to oxindole 5a

A solution of **4a** (188 mg, 0.5 mmol) in concentrated HCl (20 mL) was refluxed for 12 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate (6:1) to provide pure **5a** as a white solid (50% yield).

Mp 108–110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (t, J=7.5 Hz, 1H), 7.31 (d, J=7.0 Hz, 1H), 7.26–7.18 (m, 4H), 7.07 (t, J=7.5 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 3.71 (s, 2H), 2.42 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5, 145.4, 139.7, 134.4, 129.5, 129.0, 127.8, 127.3, 124.6, 124.3, 123.7, 122.7, 109.5, 36.1, 21.4; EIMS m/z 223 (M^+); HRMS (ESI) calcd for $C_{15}H_{14}NO$ ($[M+H]^+$), 224.1075; found, 224.1073.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 20872128) as well as the Scientific Research Fund of Educational Bureau of Zhejiang Province (20070304) for financial support of this work.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.094.

References and notes

1. (a) Trost, B. M. *Science* **1991**, *254*, 1471; (b) Hall, N. *Science* **1994**, *266*, 32; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (d) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.
2. For reviews on multicomponent reactions, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekenth, A. R.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899; (c) von Wangelin, A. J.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 4286; (d) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (f) Tejedor, D.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484.
3. (a) Hugel, H. M.; Kennaway, D. J. *Org. Prep. Proced. Int.* **1995**, *27*, 1; (b) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787; (c) Chang, J.; Heieh, H.; Chang, C.; Hsu, K.; Chiang, Y.; Chen, C.; Kuo, C.; Liou, J. *J. Med. Chem.* **2006**, *49*, 6656; (d) Liu, K. G.; Robichaud, A. J. *Drug Dev. Res.* **2009**, *70*, 145; (e) Liu, D. Y.; Zhao, G. W.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975.
4. For selected recent examples, see (a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614; (b) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311; (c) Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943; (d) Bailey, W. F.; Luderer, M. R.; Mealy, M. J. *Tetrahedron Lett.* **2003**, *44*, 5303; (e) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213; (f) Kurono, N. .; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Tetrahedron* **2004**, *60*, 1791; (g) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906; (h) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777; (i) Yip, K.-T.; Yand, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130; (j) Schintani, R.; Yamagami, T. .; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799; (k) Ma, S.; Han, X. Q.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037; (l) Fuwa, H.; Sasaki, M. *J. Org. Chem.* **2009**, *74*, 212; (m) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Miburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066; (n) Liu, K. G.; Lo, J. R.; Robichaud, A. J. *Tetrahedron* **2010**, *66*, 573.
5. The first report for ketenimine, see: Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 887.
6. For reviews on formation and synthetic applications of ketenimines, see: (a) Lu, P.; Wang, Y. G. *Synlett* **2010**, 166; (b) Yoo, E. J.; Chang, S. *Curr. Org. Chem.* **2009**, *13*, 1766; (c) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302; (d) Krow, G. R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 435.
7. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596; (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057; (c) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520.
8. (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038; (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046; (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347; (d) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897; (e) Yoo, E. J.; Chang, S. *Org. Lett.* **2008**, *10*, 1163; (f) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2836; (g) Kim, J.; Lee, Y.; Lee, J.; Do, Y.; Chang, S. *J. Org. Chem.* **2008**, *73*, 9454; (h) Yoo, E. J.; Park, S. H.; Lee, S. H.; Chang, S. *Org. Lett.* **2009**, *11*, 1155.
9. (a) Cui, S. L.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2006**, *8*, 4517; (b) Cui, S. L.; Wang, J.; Wang, Y. G. *Org. Lett.* **2007**, *9*, 5023; (c) Cui, S. L.; Wang, J.; Wang, Y. G. *Tetrahedron* **2008**, *64*, 487; (d) She, J.; Jiang, Z.; Wang, Y. G. *Synlett* **2009**, 2023; (e) Lu, W.; Song, W. Z.; Hong, D.; Lu, P.; Wang, Y. G. *Adv. Synth. Catal.* **2009**, *351*, 1768; (f) Jin, H. W.; Xu, X. L.; Gao, J. R.; Zhong, J. H.; Wang, Y. G. *Adv. Synth. Catal.* **2010**, *352*, 347.
10. (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154; (b) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157; (c) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585.
11. (a) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q. X. *Tetrahedron Lett.* **2005**, *46*, 7295; (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.
12. (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164; (b) Chen, W. M.; Li, J. J.; Fang, D. M.; Feng, C.; Zhang, C. G. *Org. Lett.* **2008**, *10*, 4565; (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.
13. (a) Padwa, A.; Crawdord, K. R. *Tetrahedron Lett.* **2002**, *43*, 7365; (b) Phillips, D. P.; Hudson, A. R.; Nguyen, B.; Lau, T. L.; McNeill, M. H.; Dalgard, J. E.; Chen, J.-H.; Penuliar, R. J.; Miller, T. A.; Zhi, L. *Tetrahedron Lett.* **2006**, *47*, 7137.
14. Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190.
15. Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863.
16. For reviews, see: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748; (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209; (c) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527.
17. For selected examples, see: (a) von Nussbaum, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3068; (b) Deppermann, N.; Thomanek, H.; Prenzel, A. H. G. P.; Maison, W. *J. Org. Chem.* **2010**, *75*, 5994; (c) Hong, P. C.; Chen, L. J.; Lai, T. Y.; Yang, H. Y.; Chiang, S. J.; Lu, Y. Y.; Tsai, P. K.; Hsu, H. Y.; Wei, W. Y.; Liao, C. B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5065.