Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Indolo[1,2-b]indazole Derivatives via Copper(I)-Catalyzed Intramolecular Amination Reaction

Jianwen Chi [a], Chenchen Hang [a], Yongming Zhu [a] & Hajime Katayama [b]

[a] College of Pharmacy, Soochow University, Suzhou, China

[b] College of Pharmacy, Kinjo Gakuin University, Nagoya, Japan

Published online: 12 Mar 2010.

To cite this article: Jianwen Chi, Chenchen Hang, Yongming Zhu & Hajime Katayama (2010) Synthesis of Indolo[1,2-b]indazole Derivatives via Copper(I)-Catalyzed Intramolecular Amination Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:8, 1123-1133, DOI: 10.1080/00397910903043017

To link to this article: http://dx.doi.org/10.1080/00397910903043017

Synthetic Communications®, 40: 1123–1133, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903043017

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF INDOLO[1,2-*b*]INDAZOLE DERIVATIVES VIA COPPER(I)-CATALYZED INTRAMOLECULAR AMINATION REACTION

Jianwen Chi,[1] Chenchen Hang,[1] Yongming Zhu,[1] and Hajime Katayama[2]

[1]*College of Pharmacy, Soochow University, Suzhou, China*
[2]*College of Pharmacy, Kinjo Gakuin University, Nagoya, Japan*

A versatile method for preparation of indolo[1,2-b]indazole derivatives was developed by using an intramolecular amination reaction of 1-aminoindoline derivatives in reaction with CuI/PHAN/K_2CO_3 (250 mol%) in 1,4-dioxane at 105°C. The method provides indoles fused with indazole rings in good yields.

Keywords: Anticancer activity; Cu(I)-catalysis; indolo[1,2-*b*]indazole; intramolecular amination

The construction of substituted pyrazolo[1,5-*a*]indole **1** has been of long-standing interest because pyrazolo[1,5-*a*]indole derivatives such as **2** (Fig. 1) have fairly potent inhibitory activity against DNA topoisomerases I and II.[1] In this study, the ring of E and F of **2** was crucial for activities.[2] Potential anticancer activity of pyrazolo[1,5-*a*]indole derivatives prompted us to examine the activity of the related structure **3**, indolo[1,2-*b*]indazole, in the hope of expanding the scope of the series of compounds. We already have reported a new method of synthesizing indolo[1,2-*b*]indazole derivatives via a palladium-catalyzed intramolecular aromatic amination reaction.[3,4] Here, we report an alternative method to construct the structure of indolo[1,2-*b*]indazoles via the copper(I)-catalyzed intramolecular reaction of 1-acetylamino-2-(2-bromophenyl)indulines (Scheme 1).

The starting material **4** was prepared from 2-(2-bromophenyl)indole derivatives by a modification of literature procedures[5–8] and acetylated to **5** because of the instability of the hydrazine derivative, **4**. By using **5a**, we investigated in detail on the copper(I)-catalyzed intramolecuar amination in a pressure tube at elevated temperature. The results are summarized in Table 1.

We used CuI as catalyst because it was shown to be efficient for the intermolecular amination of aryl halides with amides.[9–13] Our previous reports support the efficiency of this catalyst for an intramolecular amination reaction for the preparation of 1-aryl-1*H*-indazole and 2-aryl-2*H*-indazole derivatives.[14,15] Because of

Received March 25, 2009.

Address correspondence to Yongming Zhu, College of Pharmacy, Soochow University, Suzhou 215123, China. E-mail: zhuyongming@suda.edu.cn

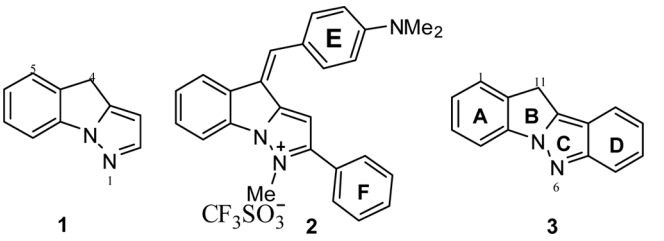
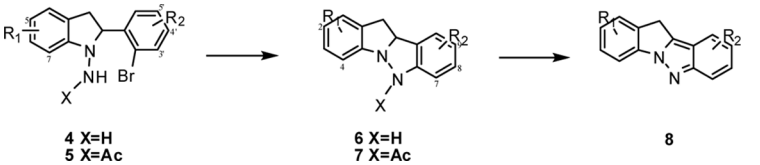


Figure 1. Skeletal structure of potential anticancer agents.



Scheme 1. Synthetic route of indolo[1,2-*b*]indazoles.

the previous experiences, we sought to find efficient reaction conditions that could solve the difficulties expected for steric hindrance of **5a**. By using **5a**, we investigated the effects of solvents, ligands, and bases (Scheme 1). Basicity was crucial. Weak bases such as K_2CO_3 provided better yield, and strong bases such as *t*-BuONa led to poor yield. Effects of ligands were investigated with 1,10-phenanthroline (PHAN), ethylenediamine (EDA), trans-1,2-cyclohexanediamine (TCHDA), and N,N′-dimethylenediamine (DMEDA) in combination with CuI, and PHAN offered the best result. Without ligand, the yield was moderate (65%). As the catalyst, CuBr

Table 1. Effects of the reaction conditions in the reaction of Cu(I)-catalyzed intramolecular amination[a]

Solvent	Metal	Ligand	Base (250 mol %)	Yield (%)[b]
Dioxane	CuI	PHAN	K_2CO_3	95
Dioxane	CuI	PHAN	Cs_2CO_3	88
Dioxane	CuI	PHAN	*t*-BuONa	22
Dioxane	CuI	EDA	K_2CO_3	68
Dioxane	CuI	TCHDA	K_2CO_3	80
Dioxane	CuI	DMEDA	K_2CO_3	71
Toluene	CuI	PHAN	K_2CO_3	83
Dioxane	CuBr	PHAN	K_2CO_3	52
Dioxane	CuI	No ligand	K_2CO_3	65
Dioxane	No metal	PHAN	K_2CO_3	<10
Dioxane	No metal	No ligand	K_2CO_3	0

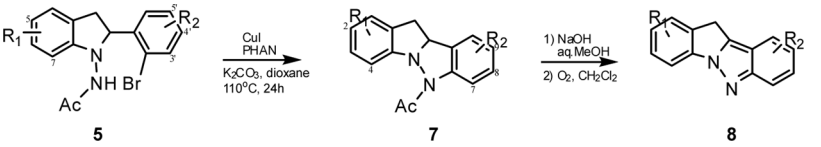
[a]Reaction conditions: A mixture of **5a** (1 mmol), CuI (0.05 mmol), ligand (0.1 mmol), base (2.5 mmol), and solvent (3 mL) in a pressure tube was heated at 110 °C for 20 h.

[b]Isolated yields after silica gel chromatography.

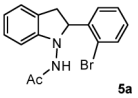
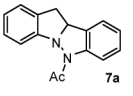
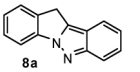
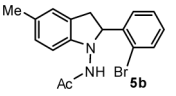
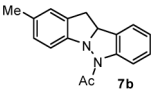
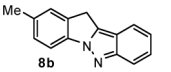
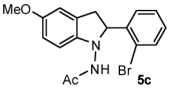
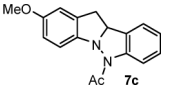
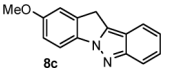
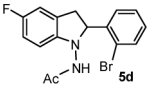
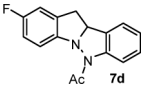
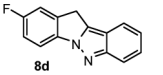
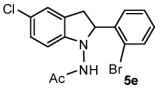
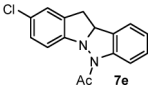
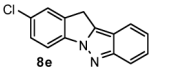
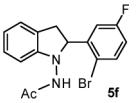
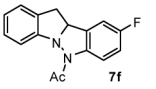
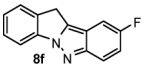
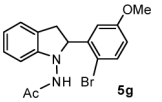
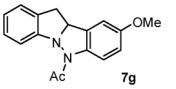
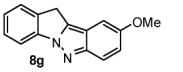
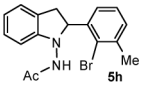
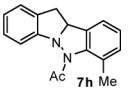
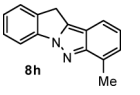
Notes. PHAN, 1,10-phenanthroline; TCHDA, *trans*-1,2-cyclohexanediamine; EDA, ethylenediamine; and DMEDA, N,N′-dimethylenediamine.

was usable but the yield was less than that with CuI. Without copper(I) catalyst, almost no reaction was observed. Optimal reaction conditions for the synthesis of indolo[1,2-*b*]indazole were found to be a combination of CuI, PHAN, and K_2CO_3 in anhydrous 1,4-dioxane as a solvent.

Table 2. Synthesis of indolo[1,2-*b*]indazole derivatives by copper(I)-catalyzed intramolecular amination[a]



5 **7** **8**

Entry	**5**	**7**	Yield (%)[b]	**8**	Yield (%)[b]
1	 **5a**	 **7a**	95	 **8a**	94
2	 **5b**	 **7b**	86	 **8b**	90
3	 **5c**	 **7c**	80	 **8c**	94
4	 **5d**	 **7d**	95	 **8d**	97
5	 **5e**	 **7e**	88[c]	 **8e**	87
6	 **5f**	 **7f**	97	 **8f**	92
7	 **5g**	 **7g**	85	 **8g**	95
8	 **5h**	 **7h**	78[c]	 **8h**	91

[a]Reaction conditions: A mixture of **5** (1 mmol), CuI (0.05 mmol), PHAN (0.1 mmol), K_2CO_3 (2.5 mmol), and 1,4-dioxane (3 mL) was reacted in a pressure tube at 110 °C for 20 h.

[b]Yields are isolated yields after chromatography.

[c]Time was prolonged to 40 h.

Optimal reaction conditions were adapted to the preparation of methyl-, methoxy-, chloro-, and fluoro-substituted indolo[1,2-*b*]indazoles, and the results are summarized in Table 2. Virtually no obvious drop of the yields was observed by introduction of a functional group to either ring A or D. The chloro group was tolerable in the reaction. Hydrolysis of **7** and subsequent air oxidation of the product **6** allowed the formation of the desired product **8** in good yield.

In summary, we have demonstrated a straightforward method for the synthesis of indolo[1,2-*b*]indazole **8** from indoline derivatives **5** via copper(I)-catalyzed intramolecular cyclization. Intramolecular C–N bond formation catalyzed by CuI was used as a key reaction to transfer **5** to **7**. This method provides a readily operable pathway for the formation of pharmacologically attractive compounds. Applications of this method to the synthesis of potential biological active compounds are now under way, and the results will be reported in due course.

EXPERIMENTAL

General Procedure for the Preparation of 5 from 4

A solution of **4** (1 mmol) and Ac_2O (2 mmol) in CH_2Cl_2 (5 mL) was stirred overnight at room temperature. The solution was neutralized using saturated Na_2CO_3 and extracted three times with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel with ethyl acetate/petroleum ether to provide the desired product as a white solid.

General Procedure for the Synthesis of 7 from 5

An oven-dried resealable Schlenk tube was charged with CuI (10 mg, 0.05 mmol, 5 mol%), 1,10-phenanthroline (18 mg, 0.1 mmol, 10 mol%), K_2CO_3 (345 mg, 2.5 mmol), and 1-acetylamino-2-(2-bromophenyl)indoline **5** (1.0 mmol), then evacuated and backfilled with argon. Anhydrous 1,4-dioxane (3 mL) was added under argon. The Schlenk tube was sealed, and the reaction mixture was stirred at 110 °C for 20 h. The resulting suspension was cooled to room temperature and filtered through a pad of silica gel, eluting with ethyl acetate. The filtrate was concentrated. Purification of the residue by chromatography on silica gel with ethyl acetate/petroleum ether provided the product **7** as a white solid.

General Procedure for the Synthesis of 8

NaOH (5 mol/L, 1.5 mL) was added to a solution of **7** (0.5 mmol) in MeOH (8 mL) and the mixture was heated to 70 °C for 30 min under a nitrogen atmosphere. The reaction mixture was poured into ice water (20 g), and the suspension was extracted with CH_2Cl_2 (25 mL × 3). The organic layer was washed with brine (30 mL × 3) and dried over Na_2SO_4. The solution was left stirring at room temperature overnight to complete air oxidation. After filtration, the filtrate was concentrated, and the residual crude product was purified by chromatography on silica gel with ethyl acetate/petroleum ether to provide the product **8** as white crystals.

SPECTRAL DATA

1-Acetylamino-2-(2-bromophenyl)indoline 5a

White solid (EtOAc); mp 186.5–187.8 °C; IR (KBr) cm^{-1}: 3229, 1667, 1488, 1254, 1023, 762. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.81 (s, 3H), 2.55 (dd, $J = 15.6$, 11.5 Hz, 1H), 3.62 (dd, $J = 14.9$, 9.1 Hz, 1H), 5.26 (s, 1H), 6.57 (d, $J = 7.1$ Hz, 1H), 6.8 (d, $J = 6.7$ Hz, 1H), 7.11 (s, 1H), 7.24 (m, 1H), 7.41 (t, $J = 7.21$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 4.6$ Hz, 1H), 9.76 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.9, 35.7, 69.6, 109.3, 120.5, 122.7, 124.5, 125.4, 127.4, 128.2, 128.5, 129.3, 132.6, 140.7, 151.2, 168.6. HRMS: calcd. for $C_{16}H_{15}\ ^{79}BrN_2O$: 330.0368; found: 330.0375.

6-Acetyl-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7a

White crystals (EtOAc); mp 130.3–132.1 °C; IR (KBr) cm^{-1}: 1662, 1596, 1482, 1465, 1392, 1318, 1278, 757; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 3.45 (d, $J = 15.6$ Hz, 1H), 3.55 (dd, $J = 15.6$, 8.1 Hz, 1H), 5.27 (d, $J = 7.9$ Hz, 1H), 6.93–7.41 (m, 7H), 7.76 (d, $J = 7.6$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 20.93, 35.69, 69.61, 109.31, 120.52, 122.68, 124.53, 125.39, 127.44, 128.17, 128.49, 129.32, 132.62, 140.67, 151.22, 168.58. HRMS: calcd. for $C_{16}H_{14}N_2O$: 250.1106; found: 250.1103.

11*H*-Indolo[1,2-*b*]indazole 8a

Yellow crystals (EtOAc); mp 168.7–170.3 °C; IR (KBr) cm^{-1} 2928, 1716, 1635, 1519, 1472, 1398, 1370, 739.1. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.11 (s, 2H), 7.11 (t, $J = 7.1$ Hz, 1H), 7.32 (t, $J = 8.1$ Hz, 2H), 7.48 (t, $J = 7.3$ Hz, 1H), 7.56 (d, $J = 7.2$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), ^{13}C NMR (400 MHz, $CDCl_3$) δ: 29.14, 112.62, 117.43, 118.71, 120.09, 122.02, 126.10, 126.49, 126.93, 128.76, 134.95, 137.76, 140.91, 153.51. HRMS: calcd. for $C_{14}H_{10}N_2$: 206.0844; found: 206.0853.

1-Acetylamino-5-methyl-2-(2-bromophenyl)indoline 5b

White solid (EtOAc); mp 185.8–188.1 °C, IR (KBr) cm^{-1}: 566, 597, 762, 1023, 1253, 1369, 1487, 1542, 1662, 3228; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.86 (s, 3H), 2.22 (s, 3H), 2.72 (d, $J = 16.0$ Hz, 1H), 3.78 (dd, $J = 10.1$, 16.3 Hz, 1H), 5.76 (d, $J = 9.7$ Hz, 1H), 6.89 (d, $J = 7.6$ Hz, 1H), 6.98 (s, 1H), 7.03 (d, $J = 8.2$ Hz, 1H), 7.29 (t, $J = 7.3$, 7.3 Hz, 1H), 7.22 (dd, $J = 6.3$, 7.5 Hz, 1H), 7.69 (d, $J = 7.6$ Hz, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 9.87 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.93, 23.34, 35.60, 109.28, 120.47, 124.52, 125.22, 125.36, 125.79, 127.41, 127.68, 129.99, 137.98, 141.16, 151.26, 168.39, 168.47. HRMS: calcd. for $C_{17}H_{17}\ ^{79}BrN_2O$: 344.0524; found: 344.0530.

6-Acetyl-2-methyl-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7b

White crystals (EtOAc); mp 136.8–128.5 °C, IR (KBr) cm^{-1}: 1667, 1475, 1388, 749, 593, 566; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H), 2.57 (s, 3H), 3.41 (d,

$J = 15.5$ Hz, 1H), 3.52 (dd, $J = 15.6$, 8.1 Hz, 1H), 5.26 (d, $J = 8.0$ Hz, 1H), 6.84–7.31 (m, 6H), 7.76 (d, $J = 7.6$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 21.37, 23.16, 33.81, 68.23, 114.55, 118.31, 122.59, 125.55, 126.14, 128.72, 129.03, 129.12, 134.16, 134.63, 139.53, 149.21, 171.72. HRMS: calcd. for $C_{17}H_{16}N_2O$: 264.1263; found: 264.1263.

2-Methyl-11*H*-indolo[1,2-*b*]indazole 8b

White crystals (EtOAc); mp 195.7–197.3 °C; IR (KBr) cm^{-1}: 3041, 2901, 1670, 1486, 1364, 1157, 818, 734. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 4.08 (s, 2H), 7.11 (t, $J = 15.1$, 7.3 Hz, 1H), 7.19–7.44 (m, 3H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.79 (dd, $J = 12.1$, 8.0 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 21.91, 28.99, 112.19, 117.52, 118.71, 119.97, 121.89, 125.55, 126.68, 127.21, 135.17, 136.51, 137.49, 138.84, 153.43. HRMS: calcd. for $C_{15}H_{12}N_2$: 220.1000; found: 220.1002.

1-Acetylamino-5-methoxy-2-(2-bromophenyl)indoline 5c

White solid (EtOAc); mp 196.8–198.2 °C; IR (KBr) cm^{-1}: 3201, 2846, 1659, 1477, 1296, 1246, 1116, 1212, 809, 757. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.82 (s, 3H), 2.27 (dd, $J = 11.7$, 15.5 Hz, 1H), 3.62 (dd, $J = 8.9$, 16.1 Hz, 1H), 3.59 (s, 3H), 5.13 (s, 1H), 6.44 (d, $J = 8.2$ Hz, 1H), 7.01 (td, $J = 4.7$, 4.7, 9.1 Hz, 2H), 7.12–7.47 (m, 3H), 7.58 (s, 1H), 9.77 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.01, 35.49, 55.43, 61.36, 108.43, 109.56, 112.67, 114.56, 118.84, 122.72, 126.68, 127.55, 131.87, 146.64, 151.23, 155.09, 168.66. HRMS: calcd. for $C_{17}H_{17}$ $^{79}BrN_2O_2$: 360.0473; found: 360.0473.

6-Acetyl-2-methoxy-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7c

White crystals (EtOAc); mp 137.3–138.7 °C; IR (KBr) cm^{-1}: 1624, 1596, 1482, 1389, 1283, 1266, 1024, 810, 775, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (s, 3H), 3.41 (d, $J = 15.6$ Hz, 1H), 3.53 (dd, $J = 8.1$, 15.6 Hz, 1H), 3.72 (s, 3H), 5.25 (d, $J = 7.9$ Hz, 1H), 6.74 (d, $J = 10.9$ Hz, 2H), 6.99 (m, 2H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.15 (t, $J = 7.07$, 7.07 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.77, 33.68, 55.89, 68.53, 109.17, 112.96, 115.35, 118.04, 124.83, 125.41, 128.23, 128.59, 134.28, 136.05, 151.64, 158.02, 171.36. HRMS: calcd. for $C_{17}H_{17}N_2O_2$: 280.1212; found: 280.1201.

2-Methoxy-11*H*-indolo[1,2-*b*]indazole 8c

Yellow solid (EtOAc); mp 210.3–211.8 °C; IR (KBr) cm^{-1}: 3063, 1603, 1634, 1485, 1435, 1264, 1246, 825, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.88 (s, 3H), 4.13 (s, 2H), 7.01 (dd, $J = 2.3$, 8.6 Hz, 1H), 7.11 (t, $J = 7.6$, 7.6, 7.6 Hz, 1H), 7.16 (d, $J = 2.1$ Hz, 1H), 7.31 (ddd, $J = 1.1$, 6.7, 8.8 Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.9$ Hz, 1H), 7.81 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 28.91, 55.88, 112.64, 112.83, 113.12, 115.5, 117.34, 118.28, 119.34, 126.11, 126.07, 134.56, 136.34, 152.98, 158.58. HRMS: calcd. for $C_{15}H_{12}N_2O$: 236.0950; found: 236.0925.

1-Acetylamino-5-fluoro-2-(2-bromophenyl)indoline 5d

White solid (EtOAc); mp 170.5–171.9 °C; IR (KBr) cm^{-1}: 3235, 2923, 1662, 1541, 1481, 1236, 1026, 761; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.81 (s, 3H), 2.57 (dd, $J = 11.6$, 15.6 Hz, 1H), 3.63 (dd, $J = 8.8$, 15.9 Hz, 1H), 5.28 (s, 1H), 6.54 (dd, $J = 8.4$, 12.8 Hz, 1H), 6.91–7.63 (m, 5H), 7.89 (d, $J = 7.1$ Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.92, 35.45, 69.98, 109.82, 122.61, 127.31, 128.17, 128.52, 129.38, 132.62, 140.36, 147.52, 155.83, 158.94, 168.47, 168.55. HRMS: calcd. for $C_{16}H_{14}$ $^{79}BrFN_2O$: 348.0274; found: 348.0270.

6-Acetyl-2-fluoro-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7d

White crystals (EtOAc); mp 174.3–175.6 °C, IR (KBr) cm^{-1}: 1681, 1483, 1381, 1343, 1244, 1178, 1127, 760; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H), 3.44 (d, $J = 15.8$ Hz, 1H), 3.54 (dd, $J = 8.1$, 15.8 Hz, 1H), 5.29 (d, $J = 8.1$ Hz, 1H), 6.85 (t, $J = 7.6$, 7.6 Hz, 2H), 6.93 (dd, $J = 4.4$, 9.5 Hz, 1H), 7.12 (t, $J = 7.3$, 7.3 Hz, 1H), 7.25 (m, 2H), 7.76 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 23.16, 33.81, 68.23, 114.55, 118.31, 122.59, 125.55, 126.14, 128.72, 129.03, 129.12, 134.16, 134.63, 139.53, 149.21, 171.72; HRMS: calcd. for $C_{16}H_{13}FN_2O$: 268.1012; found: 268.1013.

2-Fluoro-11*H*-indolo[1,2-*b*]indazole 8d

White crystals (EtOAc); mp 124.5–126.8 °C; IR (KBr) cm^{-1}: 3273, 2924, 1481, 1445, 1273, 1228, 757, 733. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.03 (s, 2H), 6.93–7.32 (m, 6H), 7.62 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 29.16, 113.19, 114.61, 117.23, 118.65, 119.85, 122.09, 122.88, 124.21, 126.87, 129.02, 130.13, 135.02, 147.64; HRMS: calcd. for $C_{14}H_9FN_2$: 224.0750; found: 224.0750.

1-Acetylamino-5-chloro-2-(2-bromophenyl)indoline 5e

Yellow solid (EtOAc); mp 185.3–187.1 °C, IR (KBr) cm^{-1}: 3073, 2927, 1645, 1602, 1463, 1390, 1267, 1217, 1172, 1030, 811, 751; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.88 (s, 3H), 2.61 (d, $J = 16.6$ Hz, 1H), 3.75 (dd, $J = 10.2$, 16.6 Hz, 1H), 5.34 (s, 1H), 6.93 (d, $J = 7.4$ Hz, 1H), 7.06 (t, $J = 8.3$, 8.3 Hz, 2H), 7.29 (td, $J = 7.1$, 7.1, 31.6 Hz, 2H), 7.71 (d, $J = 7.8$ Hz, 1H), 8.15 (dd, $J = 5.2$, 8.6 Hz, 1H), 9.60 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 23.19, 37.11, 62.64, 113.77, 116.99, 120.80, 125.48, 128.59, 129.75, 131.80, 133.39, 139.55, 141.38, 157.19, 160.37, 168.48. HRMS: calcd. for $C_{16}H_{14}$ $^{79}Br^{35}ClN_2O$: 363.9978; found: 363.9970.

6-Acetyl-2-chloro-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7e

Yellow crystals (EtOAc); mp 166.8–171.2 °C; IR (KBr) cm^{-1}: 1592, 1480, 1350, 1285, 1224, 1173, 1040, 812, 742; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 3.35 (d, $J = 15.6$ Hz, 1H), 3.46 (dd, $J = 8.7$, 15.8 Hz, 1H), 5.32 (d, $J = 8.5$ Hz, 1H), 6.95 (d, $J = 7.8$ Hz, 1H), 7.01 (d, $J = 7.6$ Hz, 1H), 7.06–7.21 (m, 3H), 7.21 (d, $J = 7.1$ Hz, 1H), 7.45 (d, $J = 14.9$, 1H), 7.51–7.68 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 23.09,

38.13, 62.91, 109.70, 113.36, 115.01, 119.66, 125.14, 127.98, 128.15, 133.73, 144.76, 150.80, 159.62, 167.44, 173.45. HRMS: calcd. for $C_{16}H_{13}{}^{35}ClN_2O$: 284.0716; found: 284.0721.

2-Chloro-11*H*-indolo[1,2-*b*]indazole 8e

Mp 145.2–146.8 °C; IR (KBr) cm^{-1}: 1601, 1517, 1474, 1445, 1409, 1372, 1272, 1228, 816, 732. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.07 (s, 2H), 7.11 (t, $J = 9.2$, 18.5 Hz, 1H), 7.25 (d, $J = 10.3$ Hz, 1H), 7.32 (t, $J = 7.5$, 15.0 Hz, 1H), 7.48 (t, $J = 7.7$, 15.3 Hz, 1H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.75 (dd, $J = 4.5$, 9.3 Hz, 1H), 7.86 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 28.96, 112.56, 116.63, 117.98, 118.26, 120.62, 126.51, 128.79, 134.87, 137.71, 140.73, 145.61, 150.75, 157.38. HRMS: calcd. for $C_{14}H_9{}^{35}ClN_2$: 240.0454; found: 240.0458.

1-Acetylamino-2-(2-bromo-5-fluorophenyl)indoline 5f

White solid (EtOAc); mp 206.8–208.7 °C; IR (KBr) cm^{-1}: 3264, 1661, 1541, 1469, 1370, 1296, 1263, 1156, 1107, 1024, 748; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.82 (s, 3H), 2.59 (dd, $J = 11.7$, 15.4 Hz, 1H), 3.64 (dd, $J = 8.8$, 15.6 Hz, 1H), 5.18 (s, 1H), 6.58 (d, $J = 8.1$ Hz, 1H), 6.83 (t, $J = 7.35$, 7.35 Hz, 1H), 7.14 (m, 3H), 7.69 (m, 2H), 9.81 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.93, 35.33, 59.89, 109.50, 120.83, 124.62, 125.32, 127.55, 134.32, 134.43, 143.32, 143.41, 150.98, 160.21, 163.45, 168.68. HRMS: calcd. for $C_{16}H_{14}{}^{79}BrFN_2O$: 348.0274; found: 348.0276.

6-Acetyl-9-fluoro-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7f

White crystals (EtOAc); mp 136.2–137.3 °C; IR (KBr) cm^{-1}: 1672, 1475, 1384, 1351, 1254, 1156, 1109, 780. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 3.43 (d, $J = 15.6$ Hz, 1H), 3.56 (dd, $J = 8.3$, 15.7 Hz, 1H), 5.27 (d, $J = 8.3$ Hz, 1H), 6.99 (m, 4H), 7.21 (dd, $J = 12.6$, 19.8 Hz, 2H), 7.70 (dd, $J = 12.6$, 19.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.82, 33.69, 67.99, 109.92, 114.77, 115.47, 115.78, 119.38, 125.12, 125.58, 128.46, 135.68, 151.32, 159.19, 162.43, 171.76. HRMS: calcd. for $C_{16}H_{13}FN_2O$: 268.1012; found: 268.1012.

9-Fluoro-11*H*-indolo[1,2-*b*]indazole 8f

Yellow solid (EtOAc); mp 187.2–188.4 °C; IR (KBr) cm^{-1}: 3066, 2918, 1646, 1525, 1473, 1298, 1170, 754. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.08 (s, 1H), 7.09 (dt, $J = 2.4$, 9.3, 9.3 Hz, 1H), 7.25 (m, 1H), 7.33 (t, $J = 7.5$, 7.5 Hz, 1H), 7.52 (m, 2H), 7.79 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 28.97, 112.58, 117.95, 118.33, 120.54, 120.67, 126.72, 128.81, 134.89, 137.64, 140.74, 150.77, 156.99, 160.17. HRMS: calcd. for $C_{14}H_9FN_2$: 224.0750; found: 224.0752.

1-Acetylamino-2-(2-bromo-5-methoxyphenyl)indoline 5g

White solid (EtOAc); mp 179.8–180.7 °C; IR (KBr) cm^{-1}: 3031, 2840, 1598, 1478, 1367, 1240, 1128, 1012, 757; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.83 (s, 3H),

2.56 (dd, $J = 12.4$, 16.0 Hz, 1H), 3.60 (dd, $J = 8.6$, 15.5 Hz, 1H), 3.76 (s, 3H), 5.12 (s, 1H), 6.58 (d, $J = 7.9$ Hz, 1H), 6.82 (dd, $J = 4.6$, 13.1 Hz, 2H), 7.12 (td, $J = 3.7$, 3.7, 7.1 Hz, 2H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.57 (d, $J = 1.5$ Hz, 1H), 9.76 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.99, 35.48, 55.42, 59.93, 109.60, 112.52, 113.43, 115.67, 120.82, 124.64, 125.53, 127.55, 133.33, 141.68, 151.23, 159.15, 168.63. HRMS: calcd. for $C_{17}H_{17}$ $^{79}BrN_2O_2$: 360.0473; found: 360.0478.

6-Acetyl-9-methoxy-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7g

White solid (EtOAc); mp 137.3–138.6 °C; IR (KBr) cm^{-1}: 1664, 1482, 1437, 1389, 1327, 1281, 1154, 868, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H), 3.42 (d, $J = 15.6$ Hz, 1H), 3.52 (dd, $J = 8.2$, 15.7 Hz, 1H), 3.73 (s, 3H), 5.23 (d, $J = 8.0$ Hz, 1H), 6.75 (m, 2H), 7.00 (dd, $J = 5.1$, 7.9 Hz, 2H), 7.16 (t, $J = 6.9$, 6.9 Hz, 2H), 7.66 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.86, 33.67, 56.09, 68.06, 108.82, 113.49, 114.67, 118.86, 124.86, 125.49, 128.28, 128.39, 133.15, 135.78, 151.56, 157.93, 171.47. HRMS: calcd. for $C_{17}H_{16}N_2O_2$: 280.1212; found: 280.1213.

9-Methoxy-11*H*-indolo[1,2-*b*]indazole 8g

Yellow solid (EtOAc); mp 199.5–201.1 °C; IR (KBr) cm^{-1}: 2999, 1641, 1462, 1348, 1217, 1020, 809, 754. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 4.08 (s, 2H), 7.00 (dd, $J = 7.1$, 21.2 Hz, 2H), 7.30 (dd, $J = 8.3$, 15.9 Hz, 1H), 7.40–7.78 (m, 3H), 7.85 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 28.86, 55.82, 96.53, 112.27, 117.15, 120.03, 121.49, 121.68, 126.18, 128.70, 134.88, 136.64, 140.98, 150.19, 155.34. HRMS: calcd. for $C_{15}H_{12}N_2O$: 236.0950; found: 236.0954.

1-Acetylamino-2-(2-bromo-3-methylphenyl)indoline 5h

Mp 188.7–191.3 °C; IR (KBr) cm^{-1}: 3191, 3049, 1666, 1545, 1475, 1373, 1248, 1255, 1020, 781, 760; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.81 (s, 3H), 2.54 (dd, $J = 9.6$, 13.6 Hz, 1H), 3.66 (dd, $J = 8.9$, 15.6 Hz, 1H), 5.33 (s, 1H), 6.56 (d, $J = 7.9$ Hz, 1H), 6.81 (t, $J = 7.3$, 7.3 Hz, 1H), 7.04–7.40 (m, 4H), 7.73 (d, $J = 5.9$ Hz, 1H), 9.72 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.79, 23.11, 35.52, 70.00, 109.05, 120.31, 124.36, 125.06, 125.23, 125.69, 127.25, 127.49, 129.82, 137.81, 141.11, 151.14, 168.29. HRMS: calcd. for $C_{17}H_{17}$ $^{79}BrN_2O$: 344.0524, found: 344.0513.

6-Acetyl-7-methyl-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7h

Mp 171.7–173.8 °C, IR (KBr) cm^{-1}: 1691, 1593, 1477, 1368, 1309, 1253, 1108, 1024, 820, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.56 (s, 3H), 3.36 (d, $J = 15.6$ Hz, 1H), 3.48 (dd, $J = 8.3$, 15.6 Hz, 1H), 5.23 (d, $J = 8.1$ Hz, 1H), 6.97 (t, $J = 7.3$, 7.3 Hz, 1H), 7.01–7.07 (m, 3H), 7.10 (dd, $J = 7.6$, 13.4 Hz, 2H), 7.16 (t, $J = 7.6$, 7.6 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 20.48, 23.51, 33.99, 68.34, 114.61, 119.84, 124.44, 125.48, 126.69, 128.23, 129.77, 131.05, 136.26, 139.90, 151.50, 153.98, 175.10. HRMS: calcd. for $C_{17}H_{16}N_2O$: 264.1263; found: 264.1266.

7-Methyl-11*H*-indolo[1,2-*b*]indazole 8h

Mp 111.6–112.2 °C; IR (KBr) cm^{-1}: 2904, 1690, 1616, 1475, 1363, 1146, 831, 753; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.70 (s, 3H), 3.99 (s, 2H), 6.98 (dd, $J = 6.9$, 8.4 Hz, 1H), 7.05 (d, $J = 6.8$, 1H), 7.25 (dd, $J = 6.8$, 14.3 Hz, 1H), 7.40–7.52 (m, 3H), 7.91 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 17.83, 28.91 112.58, 117.08, 117.40, 122.07, 125.92, 126.17, 126.31, 128.49, 128.67, 134.89, 137.94, 141.00, 153.82. HRMS: calcd. for $C_{15}H_{12}N_2$: 220.1000; found: 220.1000.

ACKNOWLEDGMENTS

This work was partially supported by the National Natural Science Foundation of China (Grants 20472062 and 20672079) and the Natural Science Foundation of Jiangsu Province (No. BK2006048).

REFERENCES

1. Katayama, H.; Kawada, Y.; Kaneko, K.; Oshiyama, T.; Takatsu, N. Synthetic inhibitors of DNA topoisomerase I and II. *Chem. Pharm. Bull.* **1999**, *47*(1), 48–53.
2. Katayama, H.; Kiryu, Y.; Kaneko, K.; Ohshima, R. Anti-cancer activities of pyrazolo[1,5-*a*]indole derivatives. *Chem. Pharm. Bull.* **2000**, *48*(11), 1628–1633.
3. Zhu, Y.-M.; Kiryu, Y.; Katayama, H. Intramolecular aromatic amination by a hydrazine group for the synthesis of indolo[1,2-*b*]indazole derivatives. *Tetrahedron Lett.* **2002**, *43*, 3577–3580.
4. Zhu, Y.-M.; Kaneko, K.; Kato, O.; Kiryu, Y.; Takatsu, N.; Shiono, K.; Katayama, H. Synthesis of indolo[1,2-*b*]indazole derivatives. *Heterocycles* **2003**, *61*, 147–162.
5. Kuehne, M. E.; Kitagawa, T. Reactions of indoles with benzyne. *J. Org. Chem.* **1964**, *29*, 1270–1273.
6. Liu, Y.-H.; McWhorter, Jr. W. W. Synthesis of 8-desbromohinckdentine A. *J. Am. Chem. Soc.* **2003**, *125*, 4240–4252.
7. Somei, M.; Yamada, F.; Morikava, H. Syntheses of serotonin, N-methylserotonin, bufotenine, and melatonin, and the first total synthesis of N-(indol-3-yl)methyl-N-methyl-5-methoxytryptamine from tryptamine through a common intermediate, 1-hydroxytryptamine. *Heterocycles* **1997**, *46*, 91–94.
8. Winter, A. H.; Thomas, S. L.; Kung, A. C.; Falvey, D. E. Photochemical generation of nitrenium ions from protonated 1,1-diarylhydrazines. *Org. Lett.* **2004**, *6*(25), 4671–4674.
9. Klapars, A.; Antilla, J. C.; Huang, H.-X.; Buchwald, S. L. A general and efficient copper catalyst for the amidation of aryl halides and the N-arylation of nitrogen heterocycles. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
10. Hosseinzadeh, R.; Tajbakhsh, M.; Alikarami, M. Copper-catalyzed N-arylation of diazoles with aryl bromides using KF/Al_2O_3: An improved protocol. *Tetrahedron Lett.* **2006**, *47*, 5203–5205.
11. Antilla, J. C.; Klapars, A.; Buchwald, S. L. The copper-catalyzed N-arylation of indoles. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.
12. Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. Copper-diamine-catalyzed N-arylation of pyrroles, pyrazoles, indazoles, imidazoles, and triazoles. *J. Org. Chem.* **2004**, *69*, 5578–5587.
13. Klapars, A.; Buchwald, S. L. Copper-catalyzed halogen exchange in aryl halides: An aromatic Finkelstein reaction. *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845.

14. Liu, R.; Zhu, Y.-M.; Qin, L. N.; Ji, S.-J. Efficient synthesis of 1-aryl-1*H*-indazole derivatives via copper(I)-catalyzed intramolecular amination reaction. *Synth. Commun.* **2008**, *38*, 249–254.
15. Liu, R.; Zhu, Y.-M.; Qin, L. N.; Ji, S.-J.; Katayama, H. Synthesis of 2-aryl-2*H*-indazoles via copper(I)-catalyzed intramolecular amination reaction. *Heterocycles* **2007**, *71*(8), 1755–1763.