HETEROCYCLES, Vol. 71, No. 8, 2007, pp. 1755 - 1763. © The Japan Institute of Heterocyclic Chemistry
Received, 20th March, 2007, Accepted, 18th May, 2007, Published online, 22nd May, 2007. COM-07-11058

# SYNTHESIS OF 2-ARYL-2*H*-INDAZOLES *VIA* COPPER(I)-CATALYZED INTRAMOLECULAR AMINATION REACTION

**Rui Liu,[a] Yong-ming Zhu,*[a] Lie-na Qin,[a] Shun-jun Ji,[a] and Hajime Katayama[b]**

[a]College of Pharmacy, Soochow University, Suzhou 215123, P. R. China zhuyongming@suda.edu.cn

[b]School of Pharmacy, Kinjo Gakuin University 2-1723, Ohmori, Moriyama-ku, Nagoya-city, Aichi, Posta code 463-8521, Japan

**Abstract** –A versatile method for the preparation of 2-aryl-2*H*-indazoles was developed by copper(I)-catalyzed intramolecular amination reaction under the conditions of [CuI/$Cs_2CO_3$(250 mol%)/1,4-dioxane/105 $^oC$] starting from *N'*-aryl-*N'*-(*o*-bromobenzyl)acetylhydrazines. The method was applied to a wide scope of substrates and afforded indazole products in high yields.

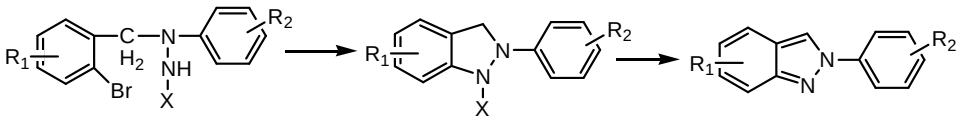
## INTRODUCTION

The indazole is an important subunit in drugs with high biological activities such as antitumor, anti-HIV, antidepressant, and contraceptive activities.[1-6] Despite of the importance of indazoles, the invention of general and efficient methods for the synthesis of fixed *N*-substituted indazoles has met with limited success, although the synthesis of *N*-aryl indazoles via a palladium-catalyzed intramolecular reaction has presented some valuable results.[7] Here we wish to describe a novel method for the synthesis of 2-aryl-2*H*-indazoles via the copper(I)-catalyzed intramolecular reaction of *N'*-aryl-*N'*-(*o*-bromobenzyl)-acetylhydrazines.

## RESULTS AND DISCUSSION

Our synthetic pathway is depicted in Scheme 1.

**Scheme 1.**




**1** X=H
**2** X=Ac

**3** X=H
**4** X=Ac

**5**

The starting material **1** was prepared from 2-bromobenzaldehydes by a modification of literature procedure.[8] The following cyclization reaction was investigated using copper(I) iodide as catalyst. Basing upon Buchwald method,[9] CuI was used for the intramolecular amination of **1a** ($R_1$,$R_2$=H), but no desired product **3a** ($R_1$,$R_2$=H) was obtained. In investigation of the experimental processes, we found that **1a** was found to be unstable in the reaction conditions, so we switched to use **2a** ($R_1$,$R_2$=H), available by acetylation of **1a**, as a starting material for cyclization.[10] This pathway provided the cyclization product **4a** ($R_1$,$R_2$=H) in high yield. The results are summarized in Table 1. Weaker base such as $K_2CO_3$ provided better yields than $Cs_2CO_3$. Strong base such as *t*-BuONa may induce side reactions with poor yield. Brief

**Table1.** Optimization of reaction conditions in copper(I)-catalyzed intramolecular amination of **2a** ( $R_1$=H, $R_2$=H )[a]

| Solvent | Cu | Ligand | Base | Yield(%)[b] |
|---|---|---|---|---|
| dioxane | CuI | 1,10-phenanthroline | $K_2CO_3$ | 93 |
| dioxane | CuI | 1,10-phenanthroline | $Cs_2CO_3$ | 86 |
| dioxane | CuI | 1,10-phenanthroline | *t*-BuONa | 25 |
| dioxane | CuI | ethylenediamine | $K_2CO_3$ | 63 |
| dioxane | CuBr | 1,10-phenanthroline | $K_2CO_3$ | 80 |
| dioxane | no metal | 1,10-phenanthroline | $K_2CO_3$ | 20 |
| toluene | CuI | 1,10-phenanthroline | $K_2CO_3$ | 85 |
| dioxane | CuI | no ligand | $K_2CO_3$ | 42 |
| dioxane | CuI | no ligand | $Cs_2CO_3$ | 95 |
| dioxane | CuI | no ligand | *t*-BuONa | 20 |
| dioxane | CuBr | no ligand | $Cs_2CO_3$ | 83 |
| dioxane | no metal | no ligand | $Cs_2CO_3$ | <10 |

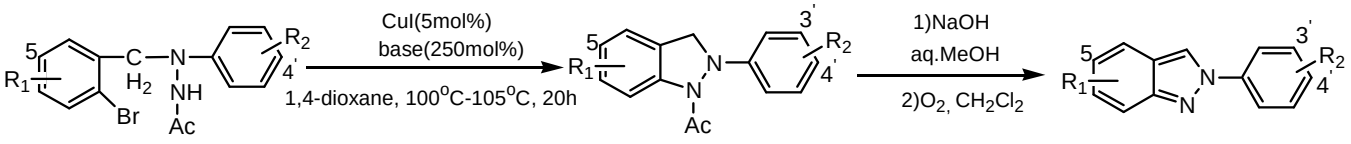
[a]Reaction was carried out in a pressure tube. A solution of **2a**, CuI, ligand and base in anhydrous solvent was heated at 100-105 $^oC$ for 20h. Cyclization product **4a** was obtained by chromatography.

[b]Isolated yields after chromatography.

studies of the effect of ligand addition was also carried out. Employment of 1,10-phenanthroline as a ligand in combination with $K_2CO_3$ yielded good result, but replacement with ethylenediamine resulted in a decrease in yields. It was also noted that the use of CuBr as catalyst slightly lowered the yield. Reaction without copper(I) catalyst led to drop the yield markedly. Anhydrous 1,4-dioxane was used as solvent affording better yield than toluene with better solubility of **2a**. When **2a** was subjected to the conditions of CuI/1,10-phenanthroline/$K_2CO_3$ at 100-105 $^oC$ for 20h in anhydrous 1,4-dioxane, **4a** was obtained in

93% yield. Reaction without ligand by CuI/$K_2CO_3$ at 100-105 $^oC$ for 20h produced **4a** in low yield 42%, but prolonged heating for 30h improved the yield up to 93%. So unnecessity of the ligand in mind, we looked into the influence of bases in reaction outcome (Table 1). The best results with 95% yield was obtained by the reaction conditions with CuI/$Cs_2CO_3$ at 100-105 $^oC$ for 20h in anhydrous 1,4-dioxane.

**Table 2.** Copper(I)-catalyzed Intramolecular amination reaction for synthesis 2-aryl-2*H*-indazoles




**2** **4** **5**

| Entry | **2** | | **4** | | Yield (%)[a] | Yield (%)[b] | **5** | | Yield (%)[c] |
|---|---|---|---|---|---|---|---|---|---|
| | $R_1$, | $R_2$ | $R_1$, | $R_2$ | | | $R_1$, | $R_2$ | |
| 1 | H, | H(2a) | H, | H(2a) | 93 | 95 | H, | H(2a) | 94 |
| 2 | H, | 4'-Me | H, | 4'-Me | 92 | 92 | H, | 4'-Me | 99 |
| 3 | H, | 4'-OMe | H, | 4'-OMe | 93 | 96 | H, | 4'-OMe | 98 |
| 4 | H, | 3'-$CF_3$ | H, | 3'-$CF_3$ | 80 | 91 | H, | 3'-$CF_3$ | 91 |
| 5 | H, | 4'-F | H, | 4'-F | 94 | 98 | H, | 4'-F | 87 |
| 6 | H, | 3'-CN | H, | 3'-CN | 87 | 87 | H, | 3'-CN | 81 |
| 7 | H, | 4'-Cl | H, | 4'-Cl | 88 | 95 | H, | 4'-Cl | 95 |
| 8 | 5-F, | H | 5-F, | H | 87 | 89 | 5-F, | H | 91 |
| 9 | 5-OMe, H | | 5-OMe, H | | 85 | 85 | 5-OMe, H | | 90 |

[a]**2a** was subjected to the reaction conditions of CuI/1,10-phenanthroline/$K_2CO_3$ at 100-105 $^oC$ for 20h in anhydrous1,4-dioxane.Isolated yields were obtained after chromatography.

[b]**2a** was subjected to the reaction conditions of CuI/$Cs_2CO_3$ at 100-105 $^oC$ for 20h in anhydrous 1,4-dioxane. Isolated yields were obtained after chromatography.

[c]Isolated yields were obtained after chromatography.

Hydrolysis of *N*-acetyl compound **4a** was effected with sodium hydroxide in aqueous methanol at 70 $^oC$ under a nitrogen atmosphere. Work-up of the reaction mixture with ice and extraction with dichloromethane gave NH product **3a** in good yield. Since the NH product was unstable, and prone to air oxidation, hydrolysis of **4a** and subsequent oxidation of the product **3a** generated indazole **5a** ($R_1$,$R_2$=H) in good yield. Thus, the general method for the synthesis of a variety of 2-aryl-2*H*-indazoles via copper(I)-catalyzed intramolecular amination reaction was established, and the result is summarized in Table 2. Since methoxy, trifluoromethyl, cyano, methyl, chloro, and fluoro groups were all tolerated

under these reaction conditions, so we found these reaction conditions were equally effective for both electron-rich and election-deficient substrates.

In summary, we are able to develope a new method for the synthesis of 2-aryl-2*H*-indazoles **5** in high yields starting from *N'*-aryl-*N'*-(*o*-bromobenzyl)acetylhydrazines **2**, which are readily prepared by a modification of literature procedure. Intramolecular C-N bond formation catalyzed by copper(I) iodide without ligand was used to transfer **2** to **4** as a key reaction. This method was simple, economical, and applicable to a wide scope of substrates affording indazole derivatives in high yields. The progress along this line of research will be reported in due course.

## EXPERIMENTAL

### General procedure for the preparation of 2 from 1:

The solution of **1** (2 mmol) and $Ac_2O$ (2 mmol) in $CH_2Cl_2$ (10 mL) was stirred at rt overnight. The solution was washed with water and dried over anhydrous sodium sulfate. After removing the solvent, residue was purified by chromatography on silica gel with petroleum EtOAc to afford white solid **2**.

### General Procedure for the synthesis of 4 from 2:

*N'*-Aryl-*N'*-(*o*-bromobenzyl)acetylhydrazine (1.0 mmol) **2**, anhydrous 1,4-dioxane (2.5 mL), CuI (10 mg, 0.05 mmol), 1,10-phenanthroline (18 mg, 0.1 mmol) / no ligand, and $K_2CO_3$ (345 mg, 2.5 mmol) / $Cs_2CO_3$ (814 mg, 2.5mmol) were placed in a pressure tube, and the tube was sealed after filling with $N_2$. Reaction was initiated by heating, and temperature was kept at 100-105 $^oC$ for 20h. Solution was filtered through Celite pad, and the filtrate was evaporated. Chromatography (silica gel, petroleum EtOAc) gave **4** as white crystals.

### General Procedure for the synthesis of 5:

To the solution of **4** (0.5 mmol) in MeOH (6 mL) was added 5mol/L NaOH (1.5 mL), and the mixture was heated to 70 $^oC$ for 30min while protected with $N_2$. The reaction mixture was poured into ice-water (20 g), and suspension was extracted with $CH_2Cl_2$ (40+20 mL). The collected solution was wash with water (30 mL×2) and dried over sodium sulfate. This solution was left stirring at rt overnight to complete air oxidation. After filtration, the filtrate was concentrated and the residual material was purified by chromatography on silica gel with petroleum EtOAc to afford **5** as solid.

***N'*-Phenyl-*N'*-(*o*-bromobenzyl)acetylhydrazine (2a):** white crystals (EtOAc), mp 76.7~77.9 $^oC$. $^1H$ NMR ( 400MHz, $CDCl_3$ ): δ 1.82 (1H, s), 2.00 (1H, s), 4.49 (1H, d, *J*=15.2 Hz), 4.82 (1H, s), 4.90 (1H, d, *J*=15.2 Hz), 6.82~6.90 (3H, m), 7.01 (3H, t, *J*=8.4 Hz), 7.17~7.28 (7H, m), 7.34 (2H, t, *J*=8.8 Hz), 7.44 (1H, d, *J*=7.6 Hz), 7.61 (2H, q, *J*=8.0 Hz). $^{13}C$ NMR (400MHz, $CDCl_3$): 19.49, 21.29, 59.75, 57.79, 113.15, 114.68, 120.26, 121.87, 128.05, 128.13, 129.49, 129.72, 130.02, 130.08, 130.34, 131.39, 133.36, 133.69, 135.19, 136.59, 149.41, 148.64, 169.64. IR: 3170, 2930, 2866, 1676, 1630, 1497, 753, 693.

HRMS: calcd for $C_{15}H_{15}N_2OBr$: 320.0347, found: 320.0275.

**1-Acetyl-2-phenyldihydroindazole (4a):** white crystals (EtOAc), mp 80~81.8 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 2.21 (3H, s), 4.56 (1H, d, *J*=11.8 Hz), 4.95 (1H, d, *J*=12.5 Hz), 7.03~7.06 (3H, m), 7.11~7.15 (2H, m), 7.27~7.29 (3H, m), 8.01 (1H, d, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 22.55, 61.52, 117.67, 122.94, 123.85, 125.50, 128.43, 128.90, 129.70, 139.90, 152.74, 171,17. IR: 2924, 2871, 1669, 1591, 1475, 757, 699. HRMS: calcd for $C_{15}H_{14}N_2O$: 238.1106, found: 238.1102.

***N'*-(4-methylphenyl)-*N'*-(*o*-bromobenzyl)acetylhydrazine:** white crystals (EtOAc), mp 161.6~163.1 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 1.80 (3H, s), 1.97 (3H, s), 2.25 (3H, s), 2.32 (3H, s), 4.40 (1H, d, *J*=14.8 Hz), 4.78 (2H, s), 4.86 (1H, d, *J*=14.4 Hz), 6.79 (1H, d, *J*=8.0 Hz), 6.92 (3H, t, *J*=8.4 Hz), 7.05 (1H, d, *J*=8.0 Hz), 7.12~7.29 (m, 8H), 7.46 (1H, d, *J*=7.6 Hz), 7.61 (2H, q, *J*=8.8 Hz) $^{13}$C NMR (400MHz, $CDCl_3$): 19.44, 20.73, 20.80, 21.26, 57.96, 60.12, 113.38, 115.04, 123.78, 124.94, 127.94, 128.00, 129.32, 129.47, 129.95, 130.14, 130.37, 130.42, 131.41, 131.60, 133.20, 133.54, 135.35, 136.75, 146.48, 147.27, 176.59. IR: 3162, 2915, 2864, 1677, 1627, 1513, 1449, 807, 746. HRMS: calcd for $C_{16}H_{17}N_2OBr$: 334.0504, found: 334.0515.

**1-Acetyl-2-(4-methylphenyl)dihydroindazole:** white crystals (EtOAc), mp 106.9~107.5 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 2.20 (3H, s), 2.33 (1H, s), 4.50 (1H, d, *J*=6.8 Hz), 4.92 (1H, d, *J*=10.8 Hz), 6.94 (2H, d, *J*=8.4 Hz), 7.07~7.14 (4H, m), 7.30 (1H, t, *J*=6.8 Hz), 8.01 (1H, d, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 20.95, 22.58, 61.73, 117.36, 117.79, 123.01, 123.05, 125.45, 128.42, 128.95, 130.24, 133.50, 139.97, 150.41, 171.09. IR: 2921, 2865, 1673, 1599, 1506, 814, 758. HRMS: calcd for $C_{16}H_{16}N_2O$: 252.1263, found: 252.1271.

***N'*-(4-Methoxyphenyl)-*N'*-(*o*-bromobenzyl)acetylhydrazine:** white crystals (EtOAc), mp 137.0~138.5 °C. $^1$H NMR (400MHz, $CDCl_3$ ): δ 1.79 (3H, s), 1.96 (3H, s), 3.75(2H, s), 3.79 (3H, s), 4.76 (2H, s), 6.83~7.00 (5H, m), 7.02 (2H, d, *J*=2.4 Hz), 7.17~7.22 (2H, m), 7.26~7.27 (4H, m), 7.38 (1H, d, *J*=7.6 Hz), 7.61 (1H, t, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 19.54, 21.40, 56.02, 56.07, 58.38, 61.24, 115.10, 115.18, 115.27, 117.37, 123.93, 125.21, 128.01, 129.40, 130.04, 130.62, 132.05, 133.24, 133.56, 135.48, 136.78, 143.03, 143.70, 154.21, 155.53, 169.71, 176.52. IR: 3183, 2947, 2903, 2829, 1678, 1635, 1509, 816, 753. HRMS: calcd for $C_{16}H_{17}N_2O_2Br$: 350.0453, found: 350.0469.

**1-Acetyl-2-(4-methoxyphenyl)dihydroindazole:** white crystals (EtOAc), mp 117.9~118.6 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 2.20 (3H, s), 3.76 (3H, s), 4.40 (1H, d, *J*=6.8 Hz), 4.89 (1H, d, *J*=7.6 Hz), 6.29 (2H, d, *J*=5.6 Hz), 6.98~7.15 (4H, m), 7.329 (1H, t, *J*=2.0 Hz), 8.02 (1H, d, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 22.67, 55.91, 62.07, 114.99, 117.24, 119.47, 123.15, 125.46, 128.48, 128.86, 140.08, 146.22, 156.64, 170.93. IR: 2908, 2831, 1671, 1602, 1501, 835, 745. HRMS: calcd for $C_{16}H_{16}N_2O_2$: 268.1212, found: 268.1213.

***N'*-(3-Trifluoromethylphenyl)-*N'*-(*o*-bromobenzyl)acetylhydrazine:** white crystals (EtOAc), mp

117.6~118.8 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 1.81 (1H, s), 1.99 (3H, s), 4.59 (1H, d, *J*=14.4 Hz), 4.89 (2H, s), 4.90 (1H, d, *J*=14.4 Hz), 6.82 (1H, s), 6.98 (2H, d, *J*=8.4 Hz), 7.10 (2H, t, *J*=8.0 Hz), 7.31~7.18 (8H, m), 7.34 (1H, t, *J*=8.4 Hz), 7.61 (1H, t, *J*=8.4 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 21.25, 57.28, 59.49, 109.49, 109.54, 111.04, 115.99, 116.68, 116.72, 117.58, 118.34, 118.36, 124.10, 128.15, 128.29, 129.91, 130.28, 130.42, 130.66, 130.46, 131.40, 132.90, 133.58, 133.85, 134.33, 135.71, 148.96, 149.68, 169.80. IR: 3260, 2999, 2360, 1672, 1614, 1508, 783, 748, 698. HRMS: calcd for $C_{16}H_{14}N_2OF_3Br$: 386.0242, found: 386.0245.

**1-Acetyl-2-(3-trifluoromethylphenyl)dihydroindazole:** white crystals (EtOAc), mp 139.0~140.6 °C. $^1$H NMR ( 400MHz, $CDCl_3$ ): δ 2.21 (3H, s), 4.58 (1H, d, *J*=14.6 Hz), 5.03 (1H, d, *J*=13.3 Hz), 7.13~7.19 (2H, m), 7.24 (1H, d, *J*=8.0 Hz), 7.28~7.36 (3H, m), 7.41 (1H, t, *J*=7.6 Hz), 7.99 (1H, d, *J*=8 Hz). $^{13}$C NMR ( 400MHz, $CDCl_3$ ): 22.53, 61.52, 114.58, 114.61, 117.88, 120.48, 122.98, 125.93, 128.50, 128.75, 130.41, 132.24, 139.68, 153.37, 171.52. IR: 2925, 2360, 1686, 1610, 1476, 793, 769, 697. HRMS: calcd for $C_{16}H_{13}N_2OF_3$: 306.0980, found: 306.0982.

***N'*-(4-Fluorophenyl)-*N'*-(*o*-bromobenzyl)acetylhydrazine:** white crystals (EtOAc), mp 139.0~140.5 °C $^1$H NMR ( 400MHz, $CDCl_3$ ): δ 1.80 (3H, s), 1.97 (3H, s), 4.39 (1H, d, *J*=14.4 Hz), 4.77 (2H, s), 4.93 (1H, d, *J*=14.4 Hz), 6.78 (2H, q, *J*=4.4 Hz), 6.81~7.06 (5H, m), 7.16~7.30 (6H, m), 7.43 (1H, d, *J*=8 Hz), 7.61 (2H, q, *J*=3.6 Hz). $^{13}$C NMR ( 400MHz, $CDCl_3$ ): 19.50, 21.32, 58.17, 60.89, 114.59, 114.67, 116.00, 116.23, 116.35, 116.57, 116.90, 116.98, 123.90, 125.11, 128.04, 128.10, 129.60, 130.23, 130.37, 131.87, 133.37, 133.65, 134.99, 136.30, 145.09, 145.93, 157.41, 156.36, 169.92, 176.84. IR: 3278, 2999, 1667, 1503, 1450, 818, 748. HRMS: calcd for $C_{15}H_{14}N_2OFBr$: 336.0274, found: 336.0260.

**1-Acetyl-2-(4-fluorophenyl)dihydroindazole:** white crystals (EtOAc), mp 111.6~112.9 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 2.19 (3H, s), 4.45 (1H, d, *J*=11.2 Hz), 4.94 (1H, d, *J*=10.8 Hz), 6.95~7.03 (4H, m), 7.11~7.16 (2H, m), 7.33 (1H, t, *J*=7.6 Hz), 8.00 (1H, d, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 22.65, 62.00, 116.29, 116.52, 117.43, 119.40, 119.48, 123.13, 125.71, 128.63, 139.76, 148.85, 172.68. IR: 2916, 1672, 1603, 1501, 854, 749. HRMS: calcd for $C_{15}H_{13}N_2OF$: 256.1012, found: 256.1018.

***N'*-(3-Cyanophenyl)-*N'*-(*o*-bromobenzyl)acetylhydrazine:** white crystals (EtOAc), mp 179.8~180.8 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 1.81 (3H, s), 2.00 (3H, s), 4.58 (1H, d, *J*=15.2 Hz), 4.81 (2H, s), 4.89 (1H, d, *J*=15.2 Hz), 6.88 (1H, s), 7.02 (2H, d, *J*=0.8 Hz), 7.041 (2H, s), 7.05~7.31 (9H, m), 7.33 (2H, t, *J*=8.0 Hz), 7.61 (2H, t, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 21.26, 57.29, 59.25, 113.49, 115.95, 117.14, 118.54, 119.68, 120.30, 123.45, 124.01, 125.06, 128.18, 130.03, 130.24, 130.58, 130.98, 131.16, 133.66, 133.92, 133.94, 135.34, 140.04, 149.07, 150.39, 155.92, 169.77. IR: 3238, 2815, 2224, 1675, 1601, 1492, 782, 748, 679. HRMS: calcd for $C_{16}H_{14}N_3OBr$: 345.0300, found: 345.0304.

**1-Acetyl-2-(3-cyanophenyl)dihydroindazole:** white crystals (EtOAc), mp 160.6~161.8 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 2.20 (3H, s), 4.54 (1H, d, *J*=12.4 Hz), 5.02 (1H, d, *J*=12.4 Hz), 7.14~7.18 (2H, m),

7.30~7.36 (4H, m), 7.41 (1H, t, *J*=7.6 Hz), 7.97 (1H, d, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 22.56, 61.42, 113.88, 117.94, 118.89, 120.84, 121.94, 122.99, 126.08, 127.41, 128.24, 128.86, 130.78, 139.44, 153.45, 171.44. IR: 2924, 2229, 1681, 1476, 1380, 795, 767, 666. HRMS: calcd for $C_{16}H_{13}N_3O$: 263.1059, found: 263.1060.

**2-(3-Cyanophenyl)-2*H*-indazole:** white crystals (EtOAc), mp 210.2~211.5 °C. $^1$H NMR (400MHz, DMSO): 7.14 (1H, t, *J*=7.6 Hz), 7.35 (1H, t, *J*=7.2 Hz), 7.68~7.75 (2H, m), 7.81 (1H, dd, *J*=8.0, 8.0Hz), 7.94 (1H, d, *J*=7.6 Hz), 8.25 (1H, d, *J*=7.6 Hz), 8.57 (1H, s), 9.16 (1H, s). $^{13}$C NMR (400MHz, $CDCl_3$): 30.87, 117.62, 119.47, 121.24, 122.04, 122.51, 122.72, 123.08, 126.93, 127.30, 130.06, 135.87, 140.11, 149.27. IR: 1666, 1628, 1584, 1480, 781, 753, 681. HRMS: calcd for $C_{14}H_9N_3$: 218.0955, found: 218.0957.

***N*'-(4-Chlorophenyl)-*N*'-(*o*-bromobenzyl)acetylhydrazine:** white crystals (EtOAc), mp 161.8~162.2 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 1.77 (3H, s), 1.98 (3H, s), 4.49 (1H, d, *J*=15.2 Hz), 4.85 (1H, d, *J*=15.6 Hz), 4.78 (2H, s), 6.75 (2H, d, *J*=8.8 Hz), 6.94 (2H, t, *J*=8.8 Hz), 7.16~7.21 (9H, m), 7.39 (1H, d, *J*=7.2 Hz), 7.61 (2H, t, *J*=9.6 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 19.42, 21.19, 57.74, 59.80, 114.35, 116.00, 123.81, 124.86, 125.01, 126.92, 128.01, 128.11, 129.47, 129.61, 129.83, 130.20, 130.22, 131.37, 133.39, 133.67, 134.73, 136.08, 147.29, 147.99, 169.72, 176.54. IR: 3158, 2931, 1676, 1626, 1492, 818, 750. HRMS: calcd for $C_{15}H_{14}N_2OClBr$ ( M-$C_2H_4ON$ ): 294.0686, found: 294.0694.

**1-Acetyl-2-(4-chlorophenyl)dihydroindazole:** white crystals (EtOAc), mp 109.1~110.5 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 2.19 (3H, s), 4.49 (1H, d, *J*=10.4 Hz), 4.94 (1H, d, *J*=11.6 Hz), 6.99 (2H, d, *J*=9.2 Hz), 7.13~7.23 (3H, m), 7.26 (1H, d, *J*=2.0 Hz), 7.32 (1H, t, *J*=8.0 Hz), 7.98 (1H, d, *J*=8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 22.59, 61.63, 117.57, 119.06, 123.03, 125.76, 128.64, 129.04, 129.75, 139.65, 151.36, 171.25. IR: 2932, 2865, 1668, 1589, 1476, 844, 760. HRMS: calcd for $C_{15}H_{13}N_2OCl$: 274.0687, found: 274.0700.

***N*'-(2-Bromo-5-fluorobenzyl)-*N*'-phenylacetylhydrazine:** white crystals (EtOAc), mp 180.4~182.0 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 1.91 (3H, s), 2.04 (3H, s), 4.53 (1H, d, *J*=15.6 Hz), 4.77 (2H, s), 4.99 (1H, d, *J*=14.2 Hz), 6.77 (3H, d, *J*=8.0 Hz), 6.86~6.91 (3H, m), 6.94~7.02 (6H, m), 7.26~7.35 (4H, m), 7.52~7.59 (2H, m). $^{13}$C NMR (400MHz, $CDCl_3$): 19.71, 21.36, 58.39, 59.79, 112.94, 114.49, 116.36, 116.56, 116.82, 117.06, 117.18, 117.27, 117.94, 118.45, 120.44, 122.07, 128.24, 128.65, 129.79, 130.19, 134.27, 134.50, 134.91, 142.92, 148.18, 148.91, 171.37, 176.65. IR: 3159, 2924, 2851, 1664, 1595, 1499, 887, 808, 700. HRMS: calcd for $C_{15}H_{14}N_2OFBr$ ( M-$C_2H_4ON$ ): 279.9960, found: 279.9987.

**5-Fluoro-1-acetyl-2-phenyldihydroindazole:** white crystals (EtOAc), mp 50.3~51.7 °C. $^1$H NMR (400MHz, $CDCl_3$): δ 2.19 (3H, s), 4.52 (1H, d, *J*=10.8 Hz), 4.96 (1H, d, *J*=27.2 Hz), 6.95 (1H, d, *J*=6.4 Hz), 7.00~7.07 (3H, m), 7.26~7.36 (3H, m), 7.95 (1H, dd, *J*=8.0, 8.0 Hz). $^{13}$C NMR (400MHz, $CDCl_3$): 22.43, 61.39, 110.46, 110.71, 114.90, 115.13, 117.62, 118.51, 121.37, 124.14, 128.26, 128.65, 129.85,

130.19. IR: 2916, 2847, 1653, 1589, 1483, 882, 810, 699. HRMS: calcd for $C_{15}H_{13}N_2OF$: 256.1012, found: 256.1008.

**5-Fluoro-2-phenyl-2*H*-indazole:** white crystals (EtOAc), mp 109.7~110.8 $^oC$. $^1H$ NMR (400MHz, $CDCl_3$): δ 7.13 (2H, q, *J*=6.8 Hz), 7.42 (1H, t, *J*=6.8 Hz), 7.54 (2H, t, *J*=8.0 Hz), 7.77 (1H, q, *J*=4.2 Hz), 7.89 (2H, d, *J*=8.0 Hz), 8.38 (1H, s). $^{13}C$ NMR (400MHz, $CDCl_3$): 118.80, 119.09, 120.42, 120.52, 120.91, 121.00, 121.29, 128.24, 128.24, 128.50, 128.60, 130.05, 130.16, 140.78. IR: 1664, 1595, 1523, 1500, 854, 812, 752, 682. HRMS: calcd for $C_{13}H_9N_2F$: 212.0750, found: 212.0742.

***N'*-(2-Bromo-5-methoxyphenzyl)-*N'*-phenylacetylhydrazine:** white crystals (EtOAc), mp 121.5~122.3 $^oC$. $^1H$ NMR (400MHz, $CDCl_3$): δ 1.94 (6H, bt, *J*=30.4 Hz), 3.73 (6H, bt, *J*=10 Hz), 4.76 (1H, s), 4.83 (1H, d, *J*=15.2 Hz), 4.97 (1H, d, *J*=15.2 Hz), 5.00 (1H, s), 6.65~6.94 (6H, m), 7.01 (2H, d, *J*=8.0 Hz), 7.04~7.13 (2H, m), 7.33 (4H, bt, *J*=7.6 Hz), 7.48 (2H, q, *J*=8.8 Hz). $^{13}C$ NMR (400MHz, $CDCl_3$): 23.13, 25.27, 52.96, 55.95, 58.24, 59.79, 113.18, 113.21, 114.52, 114.92, 115.25, 115.33, 115.40, 115.43, 116.24, 117.14, 120.44, 121.88, 128.49, 129.78, 130.09, 133.67, 133.89, 134.29, 148.62, 171.54, 172.28. IR: 3184, 2932, 1680, 1630, 1595, 1473, 872, 807, 755, 696. HRMS: calcd for $C_{16}H_{17}N_2O_2Br$ ( M-$C_2H_4ON$ ): 290.0181, found: 290.0184.

**5-Methoxy-1-acetyl-2-phenyldihydroindazole:** white crystals (EtOAc), mp 99.9~101.3 $^oC$. $^1H$ NMR (400MHz, $CDCl_3$): δ 2.18 (3H, s), 3.77 (3H, s), 4.49 (1H, d, *J*=13.2 Hz), 4.94 (1H, d, *J*=9.6 Hz), 6.70 (1H, s), 6.83 (1H, d, *J*=8.8 Hz), 7.04 (2H, d, *J*=8.0 Hz), 7.26~7.30 (3H, m), 7.90 (1H, d, *J*=8.8 Hz). $^{13}C$ NMR (400MHz, $CDCl_3$): 23.13, 25.27, 52.96, 55.95, 58.24, 59.79, 113.17, 113.21, 114.52, 114.92, 115.33, 115.33, 115.39, 115.43, 116.24, 117.14, 120.44, 121.88, 128.49, 129.78, 130.09, 133.67, 133.90, 134.29, 148.62, 171.54, 172.28. IR: 2926, 2847, 1664, 1600, 1482, 1394, 869, 811, 772, 700. HRMS: calcd for $C_{16}H_{16}N_2O_2$: 268.1212, found: 268.1205.


## ACKNOWLEDGEMENTS

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


## REFERENCES


1. J. Elguero, In *Comprehensive Heterocyclic Chemistry*; ed. by A. R. Katritzky and C. W. Rees; Pergamon Press: New York, 1984, Vol. **5**, p. 167.
2. (a) G. A. Bistochi, G. De Meo, M. Pedini, A. Ricci, H. Brouilhet, S. Bucherie, M. Rabaud, and P. Jacquignon, *Farmaco Ed. Sci.*, 1981, **36**, 315. (b) G. Picciola, F. Ravenna, G. Carenini, P. Gentili, and M. Riva, *Farmaco Ed. Sci.*, 1981, **36**, 1037.
3. B. K. Keppler and M. Hartmann, *Met.-Based Drugs*, 1994, **1**(2-3), 145.

4. (a) J.-H. Sun, C. A. Teleha, J.-S. Yan, J. D. Rodgers, and D. A. Nugiel, *J. Org. Chem*., 1997, **62**, 5627. (b) J. D. Rodgers, B. L. Johnson, H. Wang, R. A. Greenberg, S. Erickson-Viitanen, R. M. Klabe, B. C. Cordova, M. M. Rayner, G. N. Lam, and C.-H. Chang, *BioMed. Chem. Lett.*, 1996, **6**, 2919.
5. Y. Ikeda, N. Takano, H. Matsushita, Y. Shiraki, T. Koide, R. Nagashima, Y. Fujimura, M. Shindo, S. Suzuki, and T. Iwasaki, *Arzneim.-Forsch*., 1979, **29**, 511.
6. G. Corsi, G. Palazzo, C. Germani, P. S. Barcellona, and B. Silvestrini, *J. Med. Chem*., 1976, **19**, 778.
7. J. J. Song and N. K. Yee, *Org. Lett*., 2000, **2**, 519.
8. U. Lerch and J. Konig, *Synthesis*, 1983, 157.
9. A. Klapars, J. C. Antilla, X.-H. Huang, and S. L. Buchwald, *J. Am. Chem. Soc*., 2001, **123**, 7727.
10. Y.-M. Zhu, Y. Kiryu, and H. Katayama, *Tetrahedron Lett*., 2002, **43**, 3577.