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

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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.

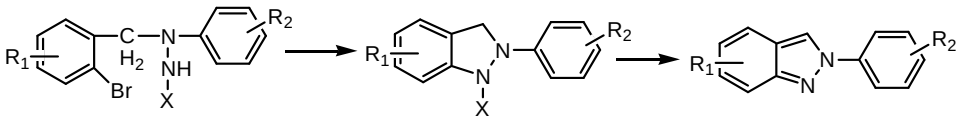
INTRODUCTION

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

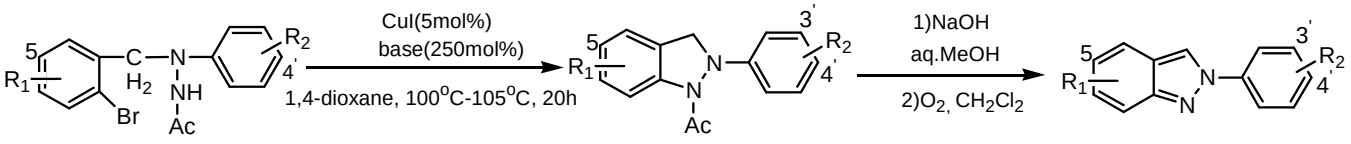
[a]Reaction was carried out in a pressure tube. A solution of **2a**, CuI, ligand and base in anhydrous solvent was heated at 100-105 ^oC for 20h. Cyclization product **4a** was obtained by chromatography.

[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.

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