# The Synthesis of Substituted Indazoles *via* Cyclization of Various Hydrazones in the Presence of Polyphosphoric Acid (PPA)



Qiu Guofu, Su Jiangtao, Feng Xichun, Wu Lamei, Xu Wenjin, Hu Xianming[#]

College of Pharmacy, Wuhan University, Wuhan 430072, P.R. China
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Research directed toward the discovery of nitric oxide synthase inhibitor led to synthesis of a series of substituted indazoles via the intramolecular cyclization of various hydrazones of substituted acetophenones and benzophenones in the presence of polyphosphoric acid (PPA). The structures of the indazoles were determined by elemental analysis, $^1$H nmr, ir, and ms.

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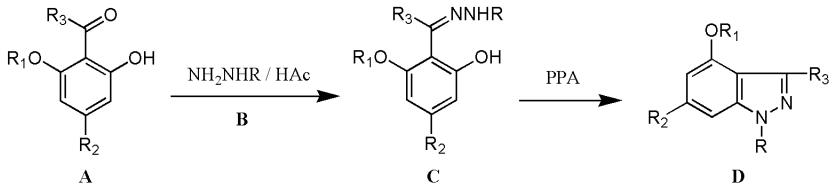
## Introduction.

The indazole nucleus, which show a widely variety of applications in the fields of agriculture, industry and biology [1,2], are seldom used but effective pharmacophore in medicinal chemistry as illustrated by their applications in pharmaceutical agents in some fields such as CNS disorder (granisetron), anti-inflammatory area (*e.g.* Bendazac and Benzydamine) [3], anti-HIV protease inhibition [4], antitumor [5,6], nitric oxide synthase inhibitors [7], male contraception [8] and binding affinity of non-steroidal progesterone receptor [9]. However, the indazole ring system is not abundant in nature, there are three classical approaches to these compounds [10]. Several improved methods have been reported [11] and a number of their derivatives have been synthesized. Since finding that indazoles were prepared from hydrazones of *o*-hydroxy (alkoxy) acetophenones in the presence of polyphosphoric acid (PPA) [12]. We further prepared a series of subsitituted indazoles, which have the potential of inhibiting nitric oxide synthases, *via* intermolecular cyclization of the hydrazones from substituted hydrazines and acetophenones or benzophenones in the presence of PPA (Figure 1).




R = H, $CH_3$, $CH_2Ph$; $R_1$ = H, $CH_3$, $C_2H_5$, n-$C_3H_7$, n-$C_4H_9$;
$R_2$ = H, $OCH_3$; $R_3$ = $CH_3$, Ph, p-Cl-Ph, p-Br-Ph, p-MeO-Ph, p-$NO_2$-Ph

Figure 1

## Result and Discussion.

According to the data shown in Table 1, we found that there was a close relation between the cyclization and structure of ketones and hydrazines. (1) The cyclization takes place selectively between the *o*-hydroxy and NH of the hydrazine moiety, when hydrazones of substituted 2-hydroxy-6-alkoxy phenones was heated in the presence of PPA. (2) The substituted groups of hydrazines have an obvious effect on temperature of cyclization. When R is $CH_3$, $PhCH_2$, H, Ph and *p*-$NO_2$Ph, the temperature used was 60 °C, 80 °C, 115 °C, 130 °C, 140 °C and 160 °C respectively. (3) When $R_3$ is aryl such as phenyl, *p*-methylphenyl, *p*-chlorophenyl or *p*-bromophenyl, the temperature required was higher than that when $R_3$ is $CH_3$. In comparison with other approaches to indazoles [11], this method has some advantages: general flexibility, selective 1-substituted products, shorter reaction times, lower reaction temperatures and moderate yields.

## EXPERIMENTAL

Melting points were measured on an XT-4 measurement devise and are uncorrected. $^1$H nmr spectra were recorded using a Varian Mercury VX-300 (300MHz) spectrometer in $CDCl_3$ solution with TMS as internal standards. Ir spectra were measured on KBr plates with a 170-SX-FT-ir spectrometer. Mass spectra were recorded on ZAB-HS (EI) Mass spectrometer. Elemental analyses were measured using a 240C elemental analysis instrument.

2,6-Dihydroxy-acetophenone and 2-hydroxy-6-alkyl-acetophenone [13] and 2-hydroxy-4,6-dimethoxyl-4'-substituted benzophenones [14] were prepared by literature methods.

Synthesis of 1-Benzyl-3-methyl-5-methoxy-indazole ($D_2$).

Benzylhydrazine (0.67 g, 5.5 mmol) was added into a solution of 2-hydroxy-6-methoxyacetophenone (0.83 g, 5 mmol), 2-3 drop of acetic acid and 95% ethanol (10 ml). The mixture was refluxed and monitored by TLC. After the reaction was finished, the mixture was distilled under reduced pressure, and a viscous residue (crude corresponding product C) was obtained. Polyphosphoric acid (PPA, 20 g) was added to the residue, and the mixture was slowly heated and stirred. When the inner

Table 1

Experimental Data of Hydrazones of Ketones in the Presence of PPA

| **B** | | **A** | | R.T. | time | **D** | |
|---|---|---|---|---|---|---|---|
| R | $R_1$ | $R_2$ | $R_3$ | (°C) | (min) | Num. | yield (%) |
| $PhCH_2$ | H | H | $CH_3$ | 80 | 15 | 1 | 32 |
| $PhCH_2$ | $CH_3$ | H | $CH_3$ | 80 | 15 | 2 | 48 |
| $PhCH_2$ | $C_2H_5$ | H | $CH_3$ | 80 | 15 | 3 | 44 |
| $PhCH_2$ | n-$C_3H_7$ | H | $CH_3$ | 80 | 15 | 4 | 42 |
| $PhCH_2$ | n-But | H | $CH_3$ | 80 | 15 | 5 | 46 |
| $PhCH_2$ | $CH_3$ | $OCH_3$ | Ph | 80 | 15 | 6 | 62 |
| $PhCH_2$ | $CH_3$ | $OCH_3$ | *p*-Me-Ph | 80 | 15 | 7 | 58 |
| $PhCH_2$ | $CH_3$ | $OCH_3$ | *p*-Br-Ph | 80 | 15 | 8 | 53 |
| $CH_3$ | H | H | $CH_3$ | 60 | 10 | 9 | 20 |
| $CH_3$ | $CH_3$ | H | $CH_3$ | 60 | 10 | 10 | 39 |
| $CH_3$ | $C_2H_5$ | H | $CH_3$ | 60 | 10 | 11 | 37 |
| $CH_3$ | n-$C_3H_7$ | H | $CH_3$ | 60 | 10 | 12 | 38 |
| $CH_3$ | n-But | H | $CH_3$ | 60 | 10 | 13 | 41 |
| H | $CH_3$ | $OCH_3$ | Ph | 115 | 30 | 14 | 56 |
| H | $CH_3$ | $OCH_3$ | *p*-Me-Ph | 115 | 30 | 15 | 53 |
| H | $CH_3$ | $OCH_3$ | *p*-Cl-Ph | 115 | 30 | 16 | 56 |
| H | $CH_3$ | $OCH_3$ | *p*-Br-Ph | 115 | 30 | 17 | 50 |
| H | $CH_3$ | $OCH_3$ | *p*-MeOPh | 140 | 60 | 18 | 54 |
| H | $CH_3$ | $OCH_3$ | *p*-$NO_2$Ph | 140 | 60 | 19 | 54 |
| Ph | $CH_3$ | $OCH_3$ | Ph | 130 | 30 | 20 | 45 |
| Ph | $CH_3$ | $OCH_3$ | *p*-Me-Ph | 130 | 30 | 21 | 48 |
| Ph | $CH_3$ | $OCH_3$ | *p*-Cl-Ph | 130 | 30 | 22 | 40 |
| Ph | $CH_3$ | $OCH_3$ | *p*-Br-Ph | 130 | 30 | 23 | 43 |
| *p*-$NO_2$Ph | $CH_3$ | $OCH_3$ | Ph | 160 | 60 | 24 | 11 |

temperature reached to about 70 °C, the mixture temperature rapidly rose to about 80 °C, and was kept at 80 °C for 15 min. After cooling, ice-water was added to the mixture and then sodium carbonate was added until a pH=7~8 was achieved. The mixture was then extracted with ethyl acetate (3×50 ml). The organic layer was then washed with water (2×20 ml), brine, dried (anhydrous $Na_2SO_4$), filtered and concentrated. The resulting oily residue was purified by chromatography over silica gel eluting with light petroleum (bp. 60-90 °C) and ethyl acetate (4:1) gave 1-benzyl-3-methyl-5-methoxy-indazole ($D_2$) (0.60 g, 48%), mp 84-86°C.

5. Synthesis of other indazoles

Other indazoles ($D_1$ and $D_{3\text{-}24}$) were obtained by a similar procedure as above. The reactants, the temperature and time of cyclization, corresponding indazoles and yields were shown in Table 1.

4-benzoyloxy-1-benzyl-3-methylindazole (**$D_1$**).

This compound is a derivative of PhCOCl and has mp.143~145 °C; $^1$H nmr: δ 7.70-8.03 (2H, m, *Ar*-H), 6.40-7.33 (11H, m, *Ar*-H), 5.15 (2H, s, >N-*$CH_2$*-), 2.43 (3H, s, Ar-*$CH_3$*); ir: $\nu_{max}$ ($cm^{-1}$): 1739 1625 1600 1576 1508 1495 1368 1351 1262 1232 1100 1060 1024 706.

*Anal.* Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.16; H, 5.31; N, 8.18. Found: C, 77.20; H, 5.73; N, 8.35.

1-Benzyl-4-methoxy-3-methylindazole (**$D_2$**).

This compound has mp 85~86 °C; $^1$H nmr: δ 7.25 (5H, s, *-Ph*), 7.20-6.97 (3H, m, *Ar*-H) 5.55 (2H,s, >N-*$CH_2$*-), 4.06 (3H, s, O*$CH_3$*), 2.70 (3H, s, Ar-*$CH_3$*); ir $\nu_{max}$ ($cm^{-1}$): 1741 1671 1622 1602 1560 1499 1446 1384 1361 1330 1283 1242 1209 1058 1015 998 895 852 697; ms (m/z, %): 252 (80.0, M).

*Anal.* Calcd. for $C_{16}H_{16}N_2O$: C, 76.15; H, 6.40; N, 11.10. Found: C, 76.42; H, 6.65; N, 11.19.

1-Benzyl-4-ethoxy-3-methyl-indazole (**$D_3$**).

This compound has mp 60~61 °C; $^1$H nmr: δ 6.87 (5H, s, *-Ph*), 5.80-6.80 (3H, m, *Ar*-H), 5.10 (2H, s, >N-*$CH_2$*-), 3.85 (2H, q, -O*$CH_2$*-), 2.50 (3H, s, Ar-*$CH_3$*), 1.37 (3H, t, -$CH_2$-*$CH_3$*); ir $\nu_{max}$ ($cm^{-1}$): 1613 1586 1507 1453 1377 1354 1264 1105 1042 777 732 699; ms (m/z, %): 266 (26.9, M).

*Anal.* Calcd. for $C_{17}H_{18}N_2O$: C, 76.65; H, 6.82; N, 10.52. Found: C, 76.34; H, 7.09; N, 10.53.

1-Benzyl-3-methyl-4-*n*-propoxy-indazole (**$D_4$**).

This compound has mp 58~59 °C; $^1$H nmr: δ 6.83 (5H, s, *-Ph*), 5.80-6.70 (3H, m, *Ar-H*), 5.07 (2H, s, >N-*$CH_2$*-), 3.75 (2H, t, -O*$CH_2$*-), 2.53 (3H, s, Ar-*$CH_3$*), 1.73 (2H, m, -*$CH_2$*$CH_3$), 1.06 (3H, t, -$CH_2$*$CH_3$*); ir $\nu_{max}$ ($cm^{-1}$): 1615 1583 1505 1475 1453 1432 1378 1355 1261 1218 1105 1070 1027 1007 905 778 732 698 671; ms (m/z, %): 280 (33.6,M).

*Anal.* Calcd. for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.20; N, 9.99. Found: C, 76.80; H, 7.10; N, 9.92.

1-Benzyl-4-*n*-butoxy-3-methyl-indazole (**$D_5$**).

This compound has mp.46~47 °C; $^1$H nmr: δ 6.85 (5H, s, *-Ph*), 5.80-6.70 (3H, m, *Ar*-H), 5.30 (2H, s, >N-*$CH_2$*-), 3.85 (2H, t, -O*$CH_2$*-), 2.50 (3H, s, Ar-*$CH_3$*), 1.15-2.03 (4H, m, -$CH_2$*($CH_2$)*$_2$$CH_3$), 0.95 (3H, t, -O($CH_2$)$_3$-*$CH_3$*); ir $\nu_{max}$ ($cm^{-1}$): 1613 1585 1507 1454 1377 1355 1255 1105 1074 777 731 699; ms (m/z, %): 294 (16.0, M).

*Anal.* Calcd. for $C_{19}H_{22}N_2O$: C, 77.50; H, 7.55; N, 9.52. Found: C, 77.40; H, 7.67; N, 9.19.

1-Benzyl-4,6-dimethoxy-3-phenyl-indazole (**$D_6$**).

This compound has mp 116~117 °C; $^1$H nmr: δ 7.00-7.99 (10H, m, *Ar*-H), 6.05 (2H, b, *Ar*-H), 5.40 (2H, s, >N-*$CH_2$*-), 3.75 (3H, s, -O*$CH_3$*), 3.65 (3H, s, -O*$CH_3$*); ir $\nu_{max}$ ($cm^{-1}$): 1616 1587 1508 1454 1406 1366 1259 1214 1152 1173 1057 1040818 769 697.

*Anal.* Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.71; H, 5.86; N, 8.13. Found: C, 76.51; H, 5.93; N, 8.15.

1-Benzyl-4,6-dimethoxy-3-(4'-methylphenyl)-indazole (**$D_7$**).

This compound has mp.145~146 °C; $^1$H nmr: δ 7.45 (2H, d, J=8 Hz, *Ar*-H), 6.77 (2H, d, J=8 Hz, *Ar*-H), 6.85 (5H, s, -$CH_2$-*Ph*), 5.77 (2H, m, *Ar*-H), 5.15 (2H, s, >N-*$CH_2$*-), 3.60 (3H, s, -O*$CH_3$*), 3.50 (3H, s, -O*$CH_3$*), 2.28 (3H, s, Ar-*$CH_3$*); ir $\nu_{max}$ ($cm^{-1}$): 1614 1587 1532 1056 1456 1405 1366 1259 1213 1191 1152 1055 1039 819 736 696.

*Anal.* Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.06; H, 6.20; N, 7.82. Found: C, 76.92; H, 6.28; N, 7.75.

3-(4'-Bromophenyl)-1-benzyl-4,6-dimethoxy-indazole (**$D_8$**).

This compound has mp 112~113 °C $^1$H nmr: δ 7.50 (2H, d, J=8 Hz, *Ar*-H), 7.33 (2H, d, J=8 Hz, *Ar*-H), 5.83 (2H, m, *Ar*-H), 5.19 (2H, s, >N-*$CH_2$*-), 3.63 (3H, s, -O*$CH_3$*), 3.56 (3H, s, -O*$CH_3$*); ir $\nu_{max}$ ($cm^{-1}$): 1619 1587 1511 1453 1400 1356 1264 1218 1155 1058 1011 831 701.

*Anal.* Calcd. for $C_{22}H_{19}BrN_2O_2$: C, 62.41; H, 4.53; N, 6.62. Found: C, 62.55; H, 4.79; N, 6.41.

4-benzoyloxy-1,3-dimethyl-indazole (**$D_9$**).

This compound is a derivative of PhCOCl and has mp.124~125 °C $^1$H nmr: δ 7.70-8.10 (2H, m, *Ar*-H), 6.43-7.37

(6H, m, *Ar*-H), 3.73 (3H, s, -N*CH*$_3$), 2.40 (3H, s, Ar-*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 1738 1704 1623 1599 1574 1507 1450 1351 1314 1253 1224 1159 1059 1065 1020 775 736 710.

*Anal.* Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.15; H, 5.31; N, 10.52. Found: C, 71.86; H, 5.34; N, 10.76.

1,3-Dimethyl-4-methoxy-indazole (**D$_{10}$**).

This compound has mp 94~95 °C $^1$H nmr: δ 5.80-6.97 (3H, m, *Ar*-H), 3.70 (6H, broad, -O*CH*$_3$, >N*CH*$_3$), 2.53 (3H, s, Ar-*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 1613 1584 1511 1439 1454 1371 1260 1193 1172 1109 1070 1010 987 778 740 692; ms (m/z, %):176 (100, M).

*Anal.* Calcd. for $C_{10}H_{12}N_2O$: C, 68.14; H, 6.88; N, 15.90. Found: C, 68.51; H, 6.90; N, 15.91.

1,3-Dimethyl-4-ethoxy-indazole (**D$_{11}$**).

This compound has mp 69~70 °C; $^1$H nmr: δ 5.70-6.93 (3H, m, *Ar*-H), 3.83 (2H, q, -O*CH*$_2$-CH$_3$), 3.65 (3H, s, >N*CH*$_3$), 2.45 (3H, s, Ar-*CH*$_3$), 1.30 (3H, t, -OCH$_2$-*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$) 1583 1511 1469 1442 1401 1373 1352 1263 1106 1072 1027 961 863 777 736 719; ms (m/z, %): 190 (78.8, M).

*Anal.* Calcd. for $C_{11}H_{14}N_2O$: C, 69.43; H, 7.43; N, 14.73. Found: C, 69.55; H, 7.70; N, 14.76.

1,3-Dimethyl-4-*n*-propoxy-indazole (**D$_{12}$**).

This compound was obtained as oil; $^1$H nmr: δ 5.80-6.93 (3H, m, *Ar*-H), 3.63-3.97 (5H, m, -N*CH*$_3$, -O*CH*$_2$-C$_2$H$_5$), 2.53 (3H, s, Ar-*CH*$_3$), 1.40-2.15 (2H, m, -OCH$_2$*CH*$_2$CH$_3$), 0.70-1.40 (3H, m, -OCH$_2$H$_2$*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 2964 2937 2877 1616 1586 1454 1379 1263 1107 1076 1051 987 777 731 639.

*Anal.* Calcd. for $C_{12}H_{16}N_2O$: C, 70.54; H, 7.91; N, 13.72. Found: C, 71.03; H, 8.41; N, 13.17.

1,3-Dimethyl-4-*n*-butoxy-indazole (**D$_{13}$**).

This compound was obtained as oil; $^1$H nmr: δ 5.70-7.00 (3H, m, *Ar*-H), 3.85 (2H, t, -O*CH*$_2$-C$_3$H$_7$), 3.73 (3H, s, -N*CH*$_3$), 2.05 (3H, s, -Ar*CH*$_3$), 1.37-1.97 (4H, m, OCH$_2$(*CH*$_2$)$_2$CH$_3$), 0.83-1.37 (3H, t, -O(CH$_2$)$_3$*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 2987 2932 2873 1615 1586 1510 1455 1378 1264 1106 1077 980 776 730 640.

*Anal.* Calcd. for $C_{13}H_{18}N_2O$: C, 71.51; H, 8.33; N, 12.83. Found: C, 12.83; H, 8.63; N, 12.60.

4,6-Dimethoxy-3-phenyl-1*H*-indazole (**D$_{14}$**).

This compound has mp 210~211 °C $^1$H nmr: δ 11.95 (1H, broad, >*N-H*), 7.90 (2H, m, *Ar*-H), 7.37 (2H, m, *Ar*-H), 6.05 (1H, d, J=2 Hz, *Ar*-H), 5.77 (1H, d, J=2 Hz, *Ar*-H), 3.80 (3H, s, -O*CH*$_3$), 3.60 (3H, s, -O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 3360-2500 1627 1597 1571 1533 1454 1386 1322 1226 1204 1152 1111 1046 1002 840 819 780 755 698; ms (m/z, %): 254(100, M).

*Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.84; H, 5.56; N, 11.02. Found: C, 70.70; H, 5.49; N, 11.29.

4,6-Dimethoxy-3-(4'-methylphenyl)-1*H*-indazole (**D$_{15}$**).

This compound has mp.186~187 °C $^1$H nmr: δ 10.93 (1H, broad, >*N-H*), 7.87 (2H, d, J=8 Hz, *Ar*-H), 7.23 (2H, d, J=8 Hz, *Ar*-H), 6.12 (1H, d, J=2 Hz, *Ar*-H), 5.95 (1H, d, J=2 Hz, *Ar*-H), 3.89 (3H, s, -O*CH*$_3$), 3.73 (3H, s, -O*CH*$_3$), 2.56 (3H, s, -Ph*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$) 3245-2662 1624 1592 1522 1450 1465 1380 1351 1297 1221 1205 1153 1096 995 838 819 736; ms (m/z, %): 268(100, M).

*Anal.* Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.61; H, 6.02; N, 10.45. Found: C, 71.51; H, 6.07; N, 10.55.

3-(4'-Chlorophenyl)- 4,6-dimethoxy-1*H*-indazole (**D$_{16}$**).

This compound has mp 193~194 °C; $^1$H nmr: δ 11.45 (1H, broad, >*N-H*), 7.90 (2H, d, J=8 Hz, *Ar*-H), 7.40 (2H, d, J=8 Hz, *Ar*-H), 6.13 (1H, d, J=2 Hz, *Ar*-H), 5.80 (1H, d, J=2 Hz, *Ar*-H), 3.80 (3H, s, -O*CH*$_3$), 3.65 (3H, s, -O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$) 3171-2500 1628 1595 1532 1469 1352 1313 1224 1204 1155 1088 1044 996 843 813 788 737; ms (m/z, %): 288(100, M).

*Anal.* Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.55; N, 9.70. Found: C, 62.62; H, 4.70; N, 9.63.

3-(4'-Bromophenyl)- 4,6-dimethoxy-1*H*-indazole (**D$_{17}$**).

This compound has mp.184~185 °C; $^1$H nmr: δ 12.33 (1H, broad, >*N-H*), 7.87 (2H, d, J=8 Hz, *Ar*-H), 7.53 (2H, d, J=8 Hz, *Ar*-H), 6.12 (1H, d, J=2 Hz, *Ar*-H), 5.77 (1H, d, J=2 Hz, *Ar*-H), 3.87 (3H, s, -O*CH*$_3$), 3.71 (3H, s, -O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$) 3149 2900 1629 1592 1534 1502 1471 1451 1394 1353 1313 1293 1224 1204 1150 1099 1046 992 840 805 785 724.

*Anal.* Calcd. for $C_{15}H_{13}BrN_2O_2$: C, 54.08; H, 3.94; N, 8.41. Found: C, 54.20; H, 3.95; N, 8.74.

4,6-Dimethoxy-3-(4'-methoxyphenyl)-1*H*-indazole (**D$_{18}$**).

This compound has mp 184~185 °C; $^1$H nmr: δ 12.06 (1H, broad, >*N-H*), 7.90 (2H, d, J=8 Hz, *Ar*-H), 6.90 (2H, d, J=8 Hz, *Ar*-H), 6.07 (1H, d, J=2 Hz, *Ar*-H), 5.73 (1H, d, J=2 Hz, *Ar*-H), 3.83 (6H, s, 2×O*CH*$_3$), 3.76 (3H, s, -O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 3116 2900 1626 1595 1534 1452 1410 1381 1356 1316 1245 1223 1206 1176 1156 1101 1033 996 842 822 787; ms (m/z, %): 284 (100, M).

*Anal.* Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.68; N, 9.85. Found: C, 68.00; H, 5.76; N, 10.09.

4,6-Dimethoxy-3-(4'-nitrophenyl)-1*H*-indazole (**D$_{19}$**).

This compound has mp 223~224 °C; $^1$H nmr: δ 12.29 (1H, broad, >*N-H*), 8.15 (2H, d, J=6 Hz, *Ar*-H), 7.20 (2H, d, J=6 Hz, *Ar*-H), 6.40 (1H, d, J=2 Hz, *Ar*-H), 6.23 (1H, d, J=2 Hz, *Ar*-H), 3.87 (3H, s, -O*CH*$_3$), 3.83 (3H, s, -O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$) 3413-2500 1627 1595 1530 1511 1453 1384 1336 1292 1223 1205 1155 1137 1105 997 938 860 827 810 760; ms (m/z, %): 299 (100, M).

*Anal.* Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.19; H, 4.39; N, 14.04. Found: C, 60.15; H, 4.31; N, 14.06.

4,6-Dimethoxy-1,3-diphenyl-indazole (**D$_{20}$**).

This compound has mp 104~105 °C $^1$H nmr: δ 7.10-7.90 (10H, m, 2×*Ph*), 6.47 (1H, d, J=2 Hz, *Ar*-H), 5.98 (1H, d, J=2 Hz, *Ar*-H), 3.69 (3H, s, -O*CH*$_3$), 3.65 (3H, s, -O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 1623 1597 1506 1455 1400 1364 1288 1207 1155 1101 1070 1047 1008 861 804 699 780; ms(m/z, %): 330 (100, M).

*Anal.* Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.33; H, 5.50; N, 8.48. Found: C, 76.33; H, 5.31; N, 8.40.

4,6-Dimethoxy-3-(4'-methylphenyl)-1-phenyl-indazole (**D$_{21}$**).

This compound has mp 149~150 °C; $^1$H nmr: δ 7.00-7.86 (9H, m, *Ar*-H), 6.55 (1H, d, J=2 Hz, *Ar*-H), 6.06 (1H, d, J=2 Hz, *Ar*-H), 3.83 (3H, s, -O*CH*$_3$), 3.75 (3H, s, -O*CH*$_3$) 2.43 (3H, s, Ar-*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 1615 1594 1504 1453 1404 1358 1288 1205 1154 1098 1043 1006 987 814 765 696; ms (m/z, %): 344 (100, M).

*Anal.* Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.71; H, 5.86; N, 8.13. Found: C, 76.78; H, 5.80; N, 8.19.

3-(4'-Chlorophenyl)-4,6-dimethoxy-1-phenyl-indazole (**$D_{22}$**).

This compound has mp 154~155 °C; $^1$H nmr: δ 7.27-8.20 (9H, m, *Ar*-H), 6.70 (1H, d, J=2 Hz, *Ar*-H), 6.30 (1H, d, J=2 Hz, *Ar*-H), 3.97 (6H, s, 2×O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 1624 1597 1506 1473 1454 1401 1363 1287 1209 1209 1160 1094 1007 990 830 802 748; ms (m/z, %): 364 (100, M).

*Anal*. Calcd. for $C_{21}H_{17}ClN_2O_2$: C, 69.13; H, 4.71; N, 7.68. Found: C, 69.37; H, 4.85; N, 7.72.

4,6-Dimethoxy-3-(4'-bromophenyl)-1-phenyl-indazole (**$D_{23}$**).

This compound has mp 149~150 °C; $^1$H nmr: δ 7.30-8.00 (9H, m, *Ar*-H), 6.63 (1H, d, J=2 Hz, *Ar*-H), 6.22 (1H, d, J=2 Hz, *Ar*-H), 3.90 (3H, s, -O*CH*$_3$), 3.85 (3H, s, -O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 1620 1597 1506 1473 1454 1400 1364 1288 1208 1160 1097 1071 1011 990 829 803 754 686.

*Anal*. Calcd. for $C_{21}H_{17}BrN_2O_2$: C, 61.62; H, 4.19; N, 6.84. Found: C, 61.90; H, 4.16; N, 6.75.

4,6-Dimethoxy-1-(4'-nitrophenyl)-3-phenyl-indazole (**$D_{24}$**).

This compound has mp 221~222 °C; $^1$H nmr: δ 6.07-8.27 (11H, m, *Ar*-H), 3.80 (6H, s, 2×O*CH*$_3$); ir $\nu_{max}$ (cm$^{-1}$): 2923 2848 1739 1620 1592 1576 1504 1347 1303 1292 1154 1112 1089 989 845 749 683 668.

*Anal.* Calcd. for $C_{21}H_{17}N_3O_4$: C, 67.18; H, 4.57; N, 11.20. Found: C, 67.04; H, 4.57; N, 11.00.

## REFERENCES AND NOTES

# Tel/Fax: 008627-87682339; e-mail: xmhu@whu.edu.cn

[1] J. Elguero, Comprehensive Heterocyclic Chemistry, Vol. 5; A. R. Katritzky, C. W. Rees, Eds., Pergamon, Oxford, 1984, pp.167-303.

[2] J. Elguero, Comprehensive Heterocyclic Chemistry, Vol. 3; A. R. Katritzky, C. W. Rees, E. F. V. Scriven Eds., Pergamon, Oxford, 1996, pp.1-75.

[3] Maryadele J. O'Neil, Ann Smith, The Merck Index 13rd. Merck Research Laboratories Division of Merck & Co., Inc, Whitehouse station, NJ, 2001.

[4] J-H Sun, C. H. Teleha, J-S Yan, J. D. Rodgers and D. A. Nugiel, *J. Org. Chem.*, **62**, 5627 (1997).

[5] M. Hartmann, M. E. Sommer, B. K. Keppler, F. Kratz and Th. Einhauder, *Journal of Inorganic Biochemistry*, **59**, 214 (1995).

[6] J. M. Clarke, *Coordination Chemistry Reviews*, **236**, 209 (2003).

[7a] P. Schumann, V. Collot, Y. Hommet, W. Gsell and F. Dauphin, *Bioorganic and Medicinal Chemistry Letters*, **11**, 1153 (2001); [b] I. Uzbay, L. Tayfun, Harbans, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **26**, 567 (2002); [c] B. E. Kalisch, B. P. Connop. K. Jhamandas, R. J. Beninger and R. J. Boegman, *Neuroscience Letters*, **219**, 75 (1996); [d] R. Van Leeuwen, R. De Vries and M. R. Dzoljic, *European Journal of Pharmacology*, **287**, 211 (1995).

[8a] C. Y. Cheng, M. Y. Mo, J. Grima, L. Saso, B. Tita and D. Mruk, *Contraception*, **65**, 265 (2002); [b] M. Bonanomi, G. Lucente and B. Silvestrini, *Contraception*, **65**, 317 (2002).

[9] P. J. Connolly, S. K. Wetter, K. N. Beers, S. C. Hamel and D. Haynes-Johnson, *Bioorganic & Medicinal Chemistry Letters*, **7**, 2551 (1997).

[10a] R. C. Elderfield, in Heterocyclic Compounds, R. C., ed, John Wiley & Sons, Inc.; New York, Vol. 5, 162 (1957); [b] L. C. Behr, R. Fusco and C. H. Jarobe, in Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings, R.H. Wiley, ed, International Wiley Science; New York, 289 (1969); [c] J. Elguero, In Comprehensive Heterocyclic Chemistry, A. R. Katritzky, C. W. Rees, eds, Pergamon Press, New York, Vol. 5, 167 (1984).

[11a] J. J. Song and N. K. Yee., *Teterahedron Letters*, **42**, 2937(2001); [b] Y-M. Zhu, Y. Kiryu and H. Katayama, , *Tetrahedron Letters*, **43**, 3577 (2002); [c] L. Tamás, K. Béla, E. Levente and S. Pál, *European Journal of Medicinal Chemistry*, **34**, 1009 (1999); [d] B. Yan and H. Gstach, *Tetrahedron Letters*, **37**, 8325 (1996); [e] V. Collot, P. Dallemagne, P. R. Bovy and S. Rault, *Tetrahedron*, **55**, 6917 (1999).

[12] Z-Q Zhong, T-S. Xu, X-N. Chen, Y-Z. Qiu, Zh. Zhang and H-W. Hu, *J. Chem. Soc. Perkin Trans.*, **1**, 1279 (1993).

[13a] A. Russell Fry Jr, In "Organic Synthesis" Coll. Vol. **3**, Horning, EC; Ed., Wiley, New York, NY, p281 (1955). [b] A. Bobik, G. M. Holder and A. J. Ryan, *J. Med. Chem.*, **20**, 1194 (1977).

[14] G-F Qiu, Z-Q. Li, J. Li, Y-Z. Qiu and H-W, Hu, *Chinese Journal of Synthetic Chemistry*, **5**, 54 (1997).