

A VERSATILE SYNTHESIS OF SUBSTITUTED INDAZOLES

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Abstract - A four-step synthetic sequence for substituted indazoles was presented from 2-acylcyclohexane-1,3-diones *via* either simultaneous or stepwise dehydration and dehydrogenation of 4-substituted 4-hydroxy-4,5,6,7-tetrahydroindazoles as a key step.

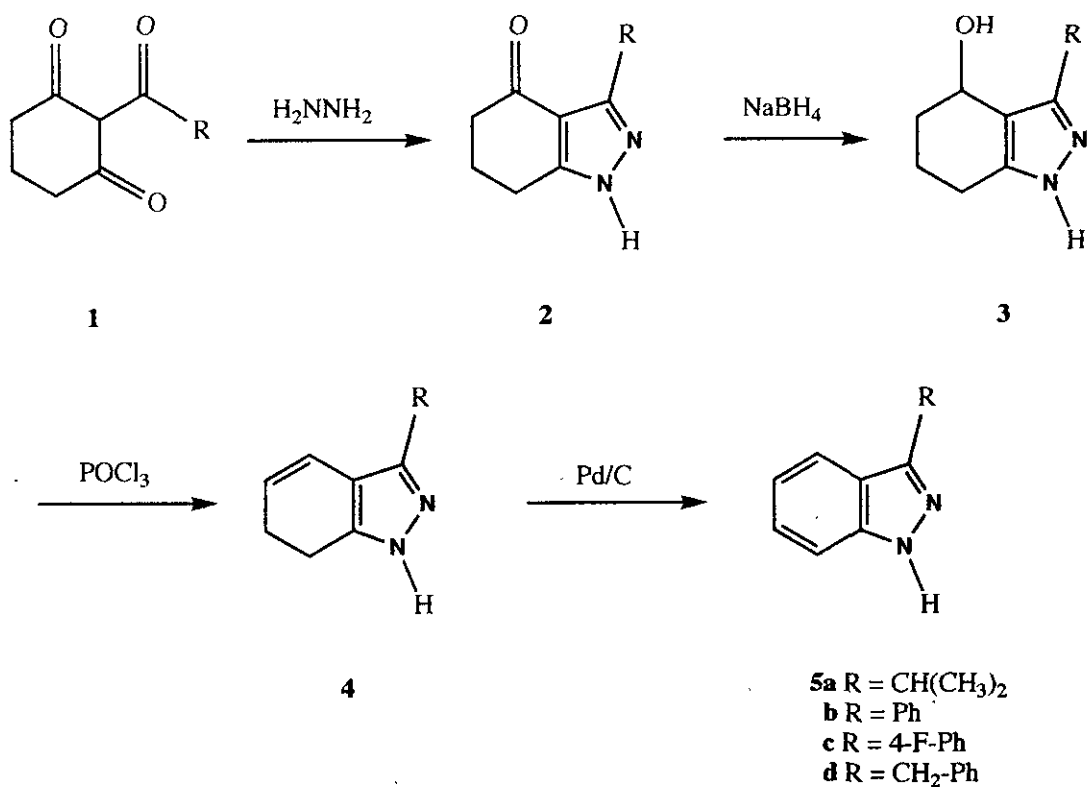
The synthetic methods for indazole nucleus are somewhat limited to involve condensation of hydrazino group,¹ generated by *in situ* reduction of diazo group in *o*-diazophenyl ketones, with C=O of the substituent at the neighboring position, and dehydrogenation of 4,5,6,7-tetrahydroindazoles.² The former method, however, is suffering from low yields, limitations of employable diazophenyl ketones,³ explosive intermediates,⁴ and the latter method is also suffering from extreme reaction conditions⁵ as well as low yields.² Other methods have been reported, but so far not so effective to overcome the limitations of introducing substituent on indazole skeletons, especially at C₃ and/or C₄.⁶ In the present paper, we describe a facile and efficient route for the preparation of indazoles, in which substituents can be easily introduced at C₃ and/or C₄.

RESULTS AND DISCUSSION

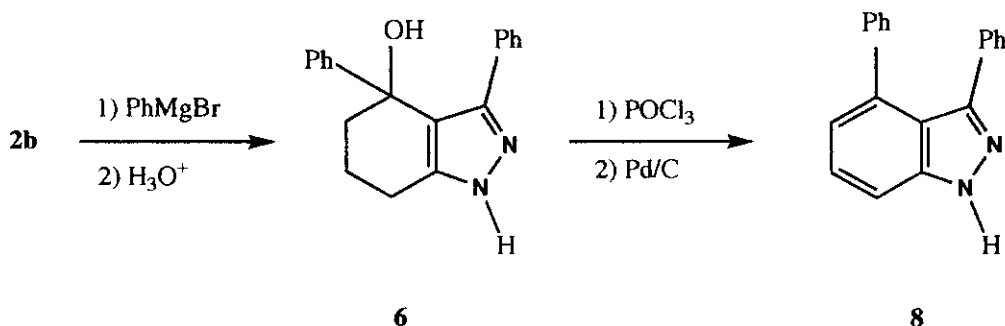
Our strategy stems from the idea that the introduction of a proper leaving group on the tetrahydroindazole system may affect the dehydrogenation step. Upon this rationale, 4-hydroxy-4,5,6,7-tetrahydroindazoles were selected as key intermediates, which may readily undergo either stepwise or simultaneous dehydration and dehydrogenation. The synthetic sequence is, thus, quite straightforward as shown in Scheme I. The prerequisite 2-acylcyclohexane-1,3-diones (1) were prepared by previously reported methods either direct acylation⁷ of cyclohexane-1,3-dione or *via* Fries rearrangement⁸ of 3-acyloxy-2-cyclohexenones⁹ in 88-92% yields. The latter procedure gave better yields, as reported.⁸ It is worthy to note that ¹³C nmr spectral data provided information for the enol-keto tautomerism on 2-acylcyclohexane-1,3-diones. The presence of one *sp*² carbon resonance (δ 112.0) and three carbonyl resonances at δ 194.9, 199.0, and 210.3 implies that keto form is the major component in compound (1a) on the ¹³C nmr scale. In the system with aromatic ring, compound (1b), however, four additional *sp*² carbon resonances appeared at δ 127.5, 128.1, 131.9, 134.2 with disappearance of the two *sp*³ carbon resonances at δ 32.1, and 37.9, representing C₄ and C₆, respectively, and one carbonyl resonance was shown at δ 198.7. This implies that enol form is the major component in compound (1b). On

the other hand, ^{13}C nmr spectrum of compound (1c) showed a pair of resonances for each carbon indicates the presence of two tautomers, which implies the keto and enol forms are at equilibrium in compound (1c). The direction of equilibrium, thus, is dependent on the substituent presumably due to the electronic effect of the substituents. The reaction of 2-acylcyclohexane-1,3-diones with hydrazine afforded 82-88% yields of 4-oxo-4,5,6,7-tetrahydroindazoles (2), which can be readily reduced by NaBH_4 to provide 4-hydroxy-4,5,6,7-tetrahydroindazoles (3) over 90% yields. The dehydration of 3 by POCl_3 ¹⁰ at 0 °C yielded 6,7-dihydroindazoles (4) over 95% yields. These dihydro systems are usually labile, thus need directly to undergo dehydrogenation for better yields. Subsequent dehydrogenation of 4 by 10% Pd/C at 100 °C in dioxane led to excellent yields of indazoles (5), whose spectral as well as elemental analysis data were satisfactory to the presented structure. On the other hand, heating 3 with catalytic amounts of *p*-TsOH in the presence of 10% Pd/C at 100 °C in dioxane afforded 4 and 5 in a ratio of 3-4:7-6 with 78-86% yields. In this step, the ratios of the products were highly dependent on reaction time. The longer reaction time increased the portion of aromatized system, which implies that dehydration step is followed by dehydrogenation step. In general, 20 h is the limit to obtain the maximum yields of indazoles (5).

Scheme 1.



In addition, the substituents at C₄ can be readily introduced by the reactions of 2 with Grignard reagents, followed by either stepwise or simultaneous dehydration and dehydrogenation.



In conclusion, the present method offers advantages over the methods,¹⁻³ previously reported. The reaction requires readily available reagents, and is applicable to the synthesis of various 3- and/or 4-substituted indazoles with high yields, as well as is able to carry out under relatively mild conditions.

EXPERIMENTAL

General. Melting points were determined on Yanaco micro melting point apparatus and are uncorrected. Ir spectra were obtained on a Perkin Elmer 1310 spectrophotometer in KBr, except where noted. Nuclear magnetic resonance (nmr) spectra were obtained on a Bruker AM-300 (300 MHz for ¹H nmr and 75.5 MHz for ¹³C nmr) spectrometer and chemical shift are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Dry pyridine was obtained by distilling over CaH₂ and all other solvents were reagent grade and used directly without further purification. The enol esters, 3-benzoyloxy-2-cyclohexenone and 3-phenylacetyloxy-2-cyclohexenone, and corresponding 2-acylcyclohexane-1,3-diones (1c) and (1d) were prepared by known methods.⁸

General Synthetic Procedure:

2-Acylcyclohexane-1,3-diones (1). To the suspension of 2.66 g (0.02 mol) of anhyd. AlCl₃ in 100 ml of freshly distilled 1,2-dichloroethane was slowly added by dropping 0.01 mol of enol ester, and resulting mixture was stirred for 2-24 h under N₂ gas at room temperature. Reaction mixture was poured into the mixture of ice and conc. H₂SO₄. Organic layer was separated and aqueous layer was extracted with CHCl₃. The combined organic layer was washed with water and dried over anhyd. MgSO₄. Evaporation of the solvent afforded pale yellow liquid, which was purified by column chromatography on silica gel, eluting with hexane:CH₂Cl₂(2:1). The early fractions provide products.

4-Oxo-4,5,6,7-tetrahydroindazoles (2). The ice-cold mixture of 0.05 g (0.01 mol) of hydrazine and 0.01 mol of 1 in 25 ml of EtOH was allowed to be stirred at room temperature for 4-6 h and the solvent removed. The crude product was purified by either column chromatography [hexane:EtOAc(3:1)] on silica gel or recrystallization from hexane:EtOAc(1:1).

4-Hydroxy-4,5,6,7-tetrahydroindazoles (3). To a stirred suspension of 0.38 g(0.01 mol) of NaBH_4 in 25 ml of EtOH was added 0.01 mol of **2**, and resulting mixture was stirred for 6-8 h. After removal of the solvent, the resulting residue was dissolved in 25 ml of CHCl_3 and washed with 20 ml of 10% AcOH. The organic layer was washed with water, and dried over anhyd. MgSO_4 . Evaporation of the solvent afforded the crude product, which was purified by recrystallization from hexane:EtOAc(1:1).

6,7-Dihydroindazoles (4). To the ice-cold solution of 0.01 mol of **3** in 25 ml of dry pyridine was added 3.06 g(0.02 mol) of POCl_3 . The resulting mixture was allowed to stand 8 h at room temperature and was heated at 80 °C for 1.5 h on water bath. The cooled mixture was poured into ice water and extracted with EtOAc. The combined organic layer was washed with water, and dried. After removal of the solvent, the residue was purified by column chromatography on silica gel [hexane:EtOAc (5:1)]. The 6,7-dihydroindazoles turn dark almost immediately after column chromatography, thus are subject to undergo dehydrogenation directly without full characterization.

Indazoles (5). Method A: A suspension of 0.01 mol of **4** and 100 mg of 10% Pd/C in 25 ml of dioxane was heated at 100 °C for 6-8 h. Removal of the catalyst and evaporation of the solvent afforded a residue, which was dissolved in 25 ml of CH_2Cl_2 and washed with water. The organic layer was concentrated and chromatographed on silica gel eluting with hexane:EtOAc(5:1). The latter fractions provide the indazoles.

Method B. A suspension of 0.01 mol of **4**, 100 mg of 10% Pd/C, and 100 mg of *p*-TsOH in 25 ml of dioxane was heated at 100 °C for 6-8 h. Work-up and purification as given in Method A gave 6,7-dihydroindazoles and indazoles.

2-Isobutyrylcyclohexane-1,3-dione (1a); Pale yellow liquid(89%). Ir(thin film) ν 2940, 2860, 1645, 1580-1500, 1410, 1310, 1240, 1180, 1130, 1080, 1040, 995, 955, 915, 870, 810, 770 cm^{-1} ; ^1H nmr(CDCl_3 , 300 MHz) δ 1.13(d, 6H, J=6.7 Hz), 2.00(quintet, 2H, J=6.4 Hz), 2.49(t, 2H, J=6.4 Hz), 2.67(t, 2H, J=6.4 Hz), 3.97(septet, 1H, J=6.7 Hz), 17.38(s, OH) ppm; ^{13}C nmr(CDCl_3 , 75.5 MHz) δ 18.7, 18.9, 33.4, 36.2, 39.0, 112.0, 194.9, 199.0, 210.3. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3$ C:65.91, H:7.74. Found C:66.03 H:7.59.

2-(4-Fluorobenzoyl)cyclohexane-1,3-dione (1c); Pale yellow liquid(86%). Ir(thin film) ν 3050, 2940, 2880, 1645, 1590-1500, 1400, 1340, 1320, 1285, 1250, 1220, 1180, 1145, 1090, 1060, 1040, 1000, 980, 920, 840, 820, 780, 770, 730, 690, 620 cm^{-1} ; ^1H nmr(CDCl_3 , 300 MHz) δ 2.03(quintet, 2H, J=6.4 Hz), 2.48(br s, 2H), 2.69(br s, 2H), 7.04(dm, 2H, J=8.6 Hz), 7.54(dm, 2H, J=8.6 Hz), 16.80(s, OH) ppm; ^{13}C nmr(CDCl_3 , 75.5 MHz) δ 18.9, 32.2, 38.09, 113.0, 114.7(d, $^3\text{J}_{\text{C-F}}=8$ Hz), 131.4(d, $^2\text{J}_{\text{C-F}}=22$ Hz), 164.9(d, $^1\text{J}_{\text{C-F}}=249$ Hz), 194.0, 196.0, 197.3; another set(enol form) δ 18.9, 32.1, 37.9, 113.0, 114.7(d, $^2\text{J}_{\text{C-F}}=22$ Hz), 127.5, 128.1, 131.0(d, $^3\text{J}_{\text{C-F}}=8$ Hz), 131.7, 134.1, 164.9(d, $^1\text{J}_{\text{C-F}}=250$ Hz), 197.3. Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{O}_3\text{F}$ C:66.66, H:4.73. Found C:67.03, H:4.28.

4-Oxo-4,5,6,7-tetrahydro-3-isopropylindazole (2a): White platelets(94%), mp 96-98 °C. Ir(thin film) ν 3150, 3080, 2940, 2860, 1625, 1555, 1475, 1410, 1350, 1315, 1290, 1260, 1175, 1150, 1100, 1070, 1055, 1025, 1010, 890, 850, 760, 720 cm^{-1} ; ^1H nmr(CDCl_3 , 300 MHz) δ 1.30(d, 6H, J=6.8 Hz), 2.10(quintet, 2H, J=6.2 Hz), 2.50(t, 2H, J=6.2 Hz), 2.82(t, 2H, J=6.2 Hz), 3.56(septet, 1H, J=6.8 Hz), 12.45(br, NH); ^{13}C nmr(CDCl_3 , 75.5 MHz) δ 20.9, 22.5, 23.5, 26.6, 39.1, 114.2, 154.9, 155.2, 194.6. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ C:67.39, H:7.92, N:15.72. Found C:67.03, H:8.02, N:15.93.

4-Oxo-4,5,6,7-tetrahydro-3-phenylindazole (2b): White platelets(89%), mp 193-194 °C. Ir(KBr) ν 3160, 3080, 2920, 1580, 1550, 1430, 1350, 1310, 1260, 1165, 1125, 1060, 1015, 970, 890, 775, 745, 690 cm^{-1} ; ^1H nmr(CDCl_3 in $\text{DMSO}-d_6$, 300 MHz) δ 2.08(quintet, 2H, J=6.2 Hz), 2.45(t, 2H, J=6.2 Hz), 2.85(t, 2H, J=6.2 Hz), 7.37(m, 3H), 8.05(m, 2H), 13.20(br s, NH); ^{13}C nmr(CDCl_3 in $\text{DMSO}-d_6$, 75.5 MHz) δ 21.3, 25.6, 36.3, 119.3, 127.1, 127.7, 131.3, 132.0, 164.8, 165.6, 195.9. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}$ C:73.57, H:5.70, N:13.20. Found C:73.63, H:6.04, N:13.17.

4-Oxo-4,5,6,7-tetrahydro-3-(4-fluorophenyl)indazole (2c): White platelets(92%), mp 223-224° C. Ir(KBr) ν 3180, 3070, 2920, 1490, 1550, 1500, 1460, 1430, 1210, 1140, 1125, 1080, 1060, 1035, 1005, 970, 890, 830, 810, 750 cm^{-1} ; ^1H nmr(CDCl_3 in $\text{DMSO}-d_6$, 300 MHz) δ 2.10(quintet, 2H, J=6.2 Hz), 2.49(t, 2H, J=6.2 Hz), 2.86(t, 2H, J=6.2 Hz), 7.08(dm, 2H, J=8.8 Hz), 8.12(dm, 2H, J=8.8 Hz), 13.05 (br, NH); ^{13}C nmr (CDCl_3 in $\text{DMSO}-d_6$, 75.5 MHz) δ 21.7, 22.9, 39.2, 113.9, 114.4(d, $^2\text{J}_{\text{C-F}}=22$ Hz), 127.5, 128.2, 130.1, 130.2(d, $^3\text{J}_{\text{C-F}}=8$ Hz), 162.4(d, $^1\text{J}_{\text{C-F}}=242$ Hz), 192.8. Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{OF}$ C:67.82, H:4.82, N:12.17. Found C:68.07, H:4.98, N:13.07.

4-Oxo-4,5,6,7-tetrahydro-3-benzylindazole (2d): White platelete(91%), mp 165-166 °C. Ir(KBr) ν 3200, 3100, 3010, 2940, 2900, 1600, 1550, 1465, 1445, 1415, 1350, 1310, 1270, 1160, 1130, 1060, 1010, 930, 890, 870, 765, 730, 695 cm^{-1} ; ^1H nmr(CDCl_3 in $\text{DMSO}-d_6$, 300 MHz) δ 2.03(quintet, 2H, J=6.2 Hz), 2.40(t, 2H, J=6.2 Hz), 2.68(t, 2H, J=6.2 Hz), 4.22(s, 2H), 7.24-7.12(m, 5H), 13.00(br s, NH); ^{13}C nmr(CDCl_3 in $\text{DMSO}-d_6$, 75.5 MHz) δ 22.1, 23.5, 32.4, 38.8, 115.1, 126.4, 128.4, 128.7, 137.7, 148.3, 154.3, 194.8. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ C:74.31, H:6.24, N:12.38. Found C:73.93, H:6.64, N:12.93.

4-Hydroxy-4,5,6,7-tetrahydro-3-isopropylindazole (3a): White platelets(95%), mp 178-180 °C. Ir(KBr) ν 3300, 3180, 2910, 2850, 1575, 1470-1420, 1350, 1260, 1060, 1030, 980, 950, 900, 825, 780, 720 cm^{-1} ; ^1H nmr(CDCl_3 in $\text{DMSO}-d_6$, 300 MHz) δ 1.32(d, 6H, J=7.0 Hz), 1.75-1.80(m, 1H), 1.82-1.87(m, 1H), 1.89-1.96(m, 1H), 2.50-2.56(m, 1H), 2.61-2.73(m, 2H), 3.17(septet, 1H, J=7.0 Hz), 4.81(br. s, OH), 4.83(d, J=6.7 Hz, H_4), 11.10(br, NH); ^{13}C nmr(CDCl_3 in $\text{DMSO}-d_6$, 75.5 MHz) δ 18.1, 21.5, 22.0, 25.6, 33.2(2 C's), 60.9, 114.2, 133.7, 140.6. Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}$ C:66.64, H:8.95, N:15.54. Found C:67.08, H:9.01, N:15.31.

4-Hydroxy-4,5,6,7-tetrahydro-3-phenylindazole (3b): White platelets(85%), mp: 212-214 °C. Ir(KBr) ν 3170-3100, 3050, 2910-2880, 1430, 1390, 1330, 1265, 1150, 1095, 1050, 980, 945, 865, 830, 755, 725, 690 cm^{-1} ; ^1H nmr(CDCl_3 in $\text{DMSO}-d_6$, 300 MHz) δ 1.69-1.79(m, 2H), 1.95-2.09(m, 2H), 2.47-2.58(m, 1H), 2.75(dt, 1H, $J=16.0, 4.5$ Hz), 4.60(d, $J=6.0$ Hz, H_4), 4.79(t, 1H, $J=5.4$ Hz), 7.26(t, 1H, $J=7.5$ Hz), 7.37(t, 2H, $J=7.5$ Hz), 7.97(dm, 2H, $J=7.5$ Hz), 12.40(br s, NH); ^{13}C nmr(CDCl_3 in $\text{DMSO}-d_6$, 75.5 MHz) δ 16.6, 32.9, 39.5, 60.2, 78.3, 108.2, 115.0, 126.4, 126.6, 127.9, 130.8, 137.1, 150.3. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$ C:72.87, H:6.59, N:13.07. Found C:73.10, H:6.65, N:12.86.

4-Hydroxy-4,5,6,7-tetrahydro-3-(4-fluorophenyl)indazole (3c): White platelets (92%), mp 236-238 °C. Ir(KBr) ν 3100, 2920, 2880, 1565, 1475, 1420, 1370, 1320, 1260, 1190, 1140, 1075, 1045, 975, 940, 895, 860, 800, 770, 705, 620 cm^{-1} ; ^1H nmr(CDCl_3 in $\text{DMSO}-d_6$, 300 MHz) δ 1.68-1.76(m, 2H), 1.91-2.04(m, 2H), 2.48-2.52(m, 1H), 2.70(dd, 1H, $J=15.0, 3.0$ Hz), 4.71(br s, OH), 4.81(d, $J=6.8$ Hz, H_4), 7.13-7.18(m, 2H), 7.95-8.02(m, 2H), 12.40(br s, NH); ^{13}C nmr(CDCl_3 in $\text{DMSO}-d_6$, 75.5 MHz) δ 16.6, 33.0, 39.5, 60.0, 108.2, 114.9(d, $^2J_{\text{C-F}}=22$ Hz), 128.3(d, $^3J_{\text{C-F}}=8$ Hz), 130.2(d, $^4J_{\text{C-F}}=3$ Hz), 138.7, 159.7, 162.4(d, $^1J_{\text{C-F}}=242$ Hz). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{OF}$ C:68.11, H:5.72, N:12.22. Found C:69.04, H:5.65, N:12.76.

4-Hydroxy-4,5,6,7-tetrahydro-3-benzylindazole (3d): White platelets(88%), mp 173-175 °C: Ir(KBr) ν 3170-3100, 2910, 1570, 1480, 1415, 1390, 1325, 1265, 1225, 1205, 1135, 1095, 1050, 970, 895, 820, 750, 710, 690 cm^{-1} ; ^1H nmr(CDCl_3 in $\text{DMSO}-d_6$, 300 MHz) δ 1.73-1.77(m, 2H), 1.81-1.90(m, 2H), 2.46-2.56(m, 1H), 2.60(dt, 1H, $J=16.0, 4.5$ Hz), 3.15(br s, OH), 4.05(AB quartet, $J = 9.6, 4.1$ Hz, 2H, benzylic H), 4.69(overlapped d, $J=6.4$ Hz, H_4), 7.21-7.35(m, 5H), 12.56(br s, NH). Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$ C:73.66, H:7.06, N:12.27. Found C:74.02, H:6.98, N:12.76.

3-Isopropyl-6,7-dihydroindazole (4a): Pale yellow oil(98%). Ir(thin film) ν 3150, 3030, 2920, 1685, 1605, 1480, 1430, 1300, 1210, 1150, 1065, 1005, 975, 910, 865, 780, 760, 725, 690 cm^{-1} ; ^1H nmr(CDCl_3 , 300 MHz) δ 1.43(d, 6H, $J=6.7$ Hz), 2.35(td, 2H, $J=8.5, 4.3$ Hz, H_6), 2.74(t, 2H, $J=8.3$ Hz, H_7), 3.65(septet, 6H, $J=6.7$ Hz), 5.66(dt, 1H, $J=9.8, 4.3$ Hz, H_5), 6.65(dd, 1H, $J=9.8, 1.8$ Hz, H_4), 10.65(br s, NH); ^{13}C nmr(CDCl_3 , 75.5 MHz) δ 20.9, 22.1, 23.6, 28.0, 113.1, 119.7, 124.0, 126.9, 130.9. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2$ C:74.03, H:8.70, N:17.27. Found C:74.10, H:8.74, N:17.16.

3-Phenyl-6,7-dihydroindazole (4b): Oil(98%). Ir(thin film) ν 3150, 3090, 3030, 2920, 1685, 1600, 1485, 1425, 1310, 1210, 1130, 1065, 1005, 975, 910, 860, 780, 760, 725, 690, 665 cm^{-1} ; ^1H nmr(CDCl_3 , 300 MHz) δ 2.36-2.43(m, 2H, H_6), 2.73(td, 2H, $J=8.3, 1.8$ Hz, H_7), 5.78(dt, $J=9.7, 4.3$ Hz, H_5), 6.64(dt, $J=9.7, 2.1$ Hz, H_4), 7.35(m, 3H), 7.57(m, 2H), 10.55(br s, NH); ^{13}C nmr(CDCl_3 , 75.5 MHz) δ 20.9, 23.6, 113.1, 119.7, 124.0, 126.9, 127.8, 128.7, 130.8, 139.1, 148.0. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2$ C:79.56, H:6.16, N:14.27. Found C:79.63, H:6.17, N:14.29.

3-(4-Fluorophenyl)indazole (5c): White platelets(95%), mp 135-136 °C. Ir(KBr) ν 3100, 1590, 1470, 1400, 1325, 1205, 1145, 1125, 1090, 990, 900, 835, 810, 770, 730 cm^{-1} : ^1H nmr(CDCl_3 , 300 MHz) δ 7.19(m, 4H), 7.31(dd, 1H, $J=8.4, 7.0$ Hz), 7.95(m, 3H), 12.04(br s, NH): ^{13}C nmr(CDCl_3 , 75.5 MHz) δ 110.3, 116.0(d, $^2J_{\text{C-F}}=22$ Hz), 120.8, 121.4, 126.9, 129.4(d, $^3J_{\text{C-F}}=8$ Hz), 129.6, 129.7, 141.7, 144.7, 162.9(d, $^1J_{\text{C-F}}=256$ Hz). Anal. Calcd for $\text{C}_{13}\text{H}_9\text{N}_2\text{F}$ C:73.57, H:4.27, N:13.20. Found C:73.63, H:4.28, N:13.17.

3-Benzylindazole (5d): White platelets(94%), mp 115-116 °C. Ir(KBr) ν 3125, 2920, 2860, 1590, 1480, 1440, 1420, 1360, 1330, 1245, 1170, 1140, 1105, 1060, 1025, 990, 930, 890, 735, 715, 690, cm^{-1} : ^1H nmr(CDCl_3 , 300 MHz) δ 4.37(s, methylene H), 7.01(m, 1H), 7.22(m, 7H), 7.49(d, $J = 8.2$ Hz, 1H), 11.35(br, NH): ^{13}C nmr(CDCl_3 , 75.5 MHz) δ 33.6, 109.9, 120.3, 120.4, 122.1, 126.3, 126.6, 128.4, 128.7, 139.0, 141.4, 145.6. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2$ C:80.74, H:5.81, N:13.45. Found C:80.66, H:5.84, N:13.50.

3,5-Diphenyl-4-hydroxy-4,5,6,7-tetrahydroindazole (6): Into 50 ml of THF containing 2.43 g(0.1 mol) of Mg turnings, a solution of 15.7 g(0.01 mol) of bromobenzene in 60 ml of THF was added with stirring. The Grignard reagent formation was completed, a solution of 6.36 g(0.03 mol) of **2b** in 80 ml of THF was added at 60 °C for 2 h. The mixture was stirred under reflux for additional 2 h and quenched by adding 50 ml of saturated NH_4Cl solution. Work up as usual afforded white platelets (86%), mp 137-138 °C: Ir(KBr) ν 3200, 2900, 1430, 1060, 980, 750, 690 cm^{-1} : ^1H nmr(CDCl_3 , 300 MHz) δ 1.87(m, 2H), 2.10(m, 2H), 2.72(m, 4H), 4.27(s, OH), 7.08(m, 5H), 7.32(m, 3H), 12.15(s, NH). Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2$ C:83.48, H:6.64, N:10.25. Found C:84.02, H:7.02, N:9.97.

3,5-Diphenyl-4,5,6,7-tetrahydroindazole (7): The same method described previously for **4** was provided semisolid as a desired product in 70% of yield. Ir(KBr) ν 3020, 2900, 1470, 1410, 1250, 1020, 720, 680 cm^{-1} : ^1H nmr(CDCl_3 , 300 MHz) δ 2.49(td, 2H, $J=8.0, J=4.8$ Hz), 2.70(t, 2H, $J=8.0$ Hz), 5.89(t, 1H, $J=4.8$ Hz), 7.01-7.24(m, 10H), 9.53(s, NH). Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2$ C:79.56, H:6.16, N:14.27. Found C:80.02, H:6.08, N:13.90.

3,5-Diphenylindazole (8): The same method described previously for **5** was provided white platelets (78%), mp > 200 °C. Ir(KBr) ν 3020, 1470, 1430, 1020, 740, 680 cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2$ C:80.39, H:5.19, N:14.42. Found C:80.44, H:5.11, N:14.45.

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REFERENCES AND NOTES

1. a) L. C. Behr, "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings," ed. by

- A. Weisseberger and E. C. Taylor, "The Chemistry of Heterocyclic Compounds", 1967, **22**, 289,
b) H. D. Porter and W. D. Peterson, *Org. Syn., Coll. Vol. III*, 1955, 660, c) A. O. Fitton
and R. K. Smalley, "Practical Heterocyclic Chemistry," Academic Press, New York, 1968, 44.
2. a) J. P. Burnett and C. Ainsworth, *J. Org. Chem.*, 1958, **23**, 1382; b) F. Piozzi, A. Umani-Ronchi,
and L. Merlini, *Gazz. Chim. Ital.*, 1965, **95**, 814.
3. In general, the reactions are successful only for benzenediazonium salts with electron
withdrawing group on the benzene ring; R. C. Elderfied, "Heterocyclic Chemistry," Vol 5,
R. C. Elderfied, ed., Wiley, New York, 1957, 171.
4. R. Huisgen and H. Nakaten, *Ann. Chem.*, 1951, **573**, 181.
5. H. O. House, "Modern Synthetic Reactions", 2nd. ed., W. A. Benjamin, Inc., 1972, pp34-44.
6. a) C. Ruchardt and V. Hassmann, *Liebigs Ann. Chem.*, 1980, 908, b) R. Huisgen and K. Bast,
Org. Syn., Coll. Vol. V, 1973, 650, and references therein.
7. a) H. Smith, *J. Chem. Soc.*, 1953, **803**, 803; b) N. A. Rogers and H. Smith, *J. Chem. Soc.*, 1955,
341; c) L. De. Buyck, N. Schamp, and R. Verhe, *Tetrahedron Lett.*, 1975, 2491.
8. A. A. Akherm, F. A. Lakhvich, S. I. Budai, T. S. Khlebnicova, and I. I. Peterusevich,
Synthesis, 1978, 925.
9. 3-Acyloxy-2-cyclohexenones were prepared by employing methods described in W. Theilacker and
W. Schmid, *Liebigs Ann. Chem.*, 1950, **570**, 1. Spectral data of unreported compounds are
described in B. C. Kim, J. -I. Kim, and Y. Jahng, *Bull. Kor. Chem. Soc.*, 1994, **15**, 97.
10. K. L. Rinehart and E. G. Perkins, *Org. Syn., Coll. Vol. IV*, 1963, 444.

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