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Communications

A Versatile Synthesis of 3-Substituted Indazoles

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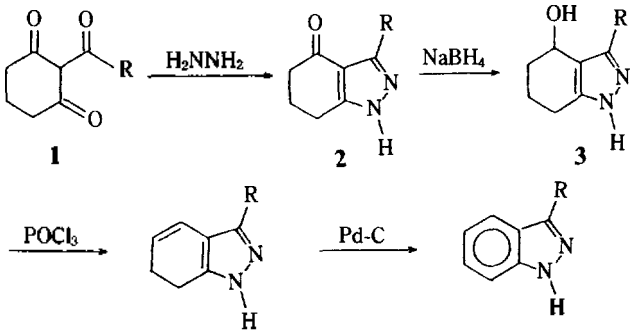
The synthetic methods for indazole nucleus are somewhat limited to involve condensation of hydrazino group[1], generated by *in situ* reduction of diazo group on *o*-diazophenyl ketones, with carbonyl group of the substituent at *ortho*-position and dehydrogenation of 4,5,6,7-tetrahydroindazoles[2]. These methods as well as others[3], however, are suffering from low yields, limitations of employable diazophenyl ketones[4], explosive intermediates[5], and extreme reaction conditions[2]. Moreover, the procedures[1,2,3,4,5] reported so far, faced difficulties in introducing substituents on the indazole skeleton.

In the present paper, we describe a facile and efficient route for the preparation of 3-substituted indazoles. Our strategy stems from the idea that the introduction of a proper leaving group on the tetrahydroindazole system may affect the dehydrogenation step. The synthetic sequence employs 4-hydroxy-4,5,6,7-tetrahydroindazles as key intermediates, which may readily undergo either stepwise or simultaneous dehydration and dehydrogenation.

The prerequisite 2-acylcyclohexane-1,3-diones **1**,[6] were treated with hydrazine[7] to afford 4-oxo-4,5,6,7-tetrahydroindazoles[8] **2** in 82-88%. The reduction of **2** by $NaBH_4$ provided 4-hydroxy-4,5,6,7-tetrahydroindazoles[8] **3** over 90% yields. The dehydration of **3** by $POCl_3$ at 0℃ [9] yielded 6,7-dihydroindazoles[8] **4**, which can be readily aromatized in the presence of 10% Pd/C at 100℃ in dioxane to give excellent yields of 3-substituted indazoles[8] **5**. On the other hand, heating **3** with catalytic amounts of *p*-TsOH in the presence of 10% Pd/C at 100℃ 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. In general, 20 h is the limit to obtain the maximum yields of indazoles **5**.



1 **2** **3** **4**

5a R=$(CH_3)_2$CH-
b R=Ph-
c R=4-F-Ph-
d R=Ph-CH_2-

In conclusion, the present method offers advantages over the methods[1,2,3], previously reported. The reaction requires readily available reagents, and is applicable to the synthesis of various 3-substituted indazoles with high yields, as well as, is able to be carried out under relatively mild conditions.

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4. In general, the reactions are successful only for benzenediazonium salts with electron withdrawing group on the

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7. Phenylhydrazine and other hydrazines are also reacted with **1** to afford 1-substituted 4-oxo-4,5,6,7-tetrahydroindazoles over 85% yields.
8. All new compounds were fully characterized by spectroscopic methods as well as elemental analysis. **4-Oxo-3-phenyl-4,5,6,7-tetrahydroindazole (2b)**: Colorless plates (89%), mp. 193-194℃; IR (KBr) ν 3160, 3080, 2920, 1580, 1550, 1430, 1350, 1310, 1260, 1165, 1125, 1060, 1015, 970, 890, 775, 745, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$ in 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 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. **4-Hydroxy-3-phenyl-4,5,6,7-tetrahydroindazole (3b)**: Colorless platelets (85%), mp. 212-214℃; IR (KBr) ν 3170-3100, 3050, 2910-2880, 1430, 1390, 1330, 1265, 1150, 1095, 1050, 980, 945, 865, 830, 755, 725, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$ in 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, 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 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. **3-Phenyl-6,7-dihydroindazole (4b)**: Pale yellow 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}; ^{1}H-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 $C_{13}H_{12}N_2$ C: 79.56, H: 6.16, N: 14.27; Found C: 79.63, H: 6.17, N: 14.29. **3-Isopypylindazole (5a)**: Colorless platelets (93%), mp. 103-104℃ (lit.[10]: 102-104℃). Unreported spectral data are: IR (KBr) ν 3060, 2950, 1605, 1570, 1525, 1480, 1440, 1355, 1290, 1225, 1165, 1140, 1115, 1095, 1060, 1040, 990, 900, 785, 760, 730 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.47 (d, 6H, J=7.0 Hz), 3.45 (septet, 1H, J=7.0 Hz), 7.08 (t, 1H, J=8.0 Hz), 7.33 (m, 2H), 7.75 (d, 1H), 11.05 (br., NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 22.1, 27.8, 109.9, 119.8, 120.6, 121.1, 126.4, 141.5, 151.8, **3-Phenylindazole (5b)**: Colorless crystals (96%), mp. 110-112℃ (lit.[11]; 106-107℃). Unreported spectral data are as follows: IR (KBr) ν 3120, 3050, 1595, 1530, 1465, 1325, 1245, 1120, 1090, 1060, 1020, 995, 980, 895, 765, 725, 685 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, 1H, J=8.1 Hz), 7.20 (t, 1H, J=8.1 Hz), 7.31 (td, 1H, J=8.1, 1.8 Hz), 7.48 (td, 1H, J=7.5, 2.1 Hz), 7.56 (td, 2H, J=7.6, 1.0 Hz), 8.05 (d, 1H, J=8.1 Hz), 8.07 (dd, 2H, J=8.1, 1.2 Hz), 12.40 (br.s, NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 110.5, 120.9, 121.2, 126.6, 127.8, 128.1, 129.0 (2 C's), 133.6, 141.7, 145.5. **3-(4-Fluorophenyl)indazole (5c)**: Colorless platelets (95%), mp. 135-136℃. IR (KBr) ν 3100, 1590, 1470, 1400, 1325, 1205, 1145, 1125, 1090, 990, 900, 835, 810, 770, 730 cm^{-1}; ^{1}H-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, $^2J_{C\text{-}F}$=22 Hz), 120.8, 121.4, 126.9, 129.4 (d, $^3J_{C\text{-}F}$=8 Hz), 129.6, 129.7, 141.7, 144.7, 162.9 (d, $^1J_{C\text{-}F}$=256 Hz). Anal. Calcd. for $C_{13}H_9N_2F$ C: 73.57, H: 4.27, N: 13.20; Found C: 73.63, H: 4.28, N: 13.17. **3-Benzylindazole (5d)**: Colorless platelets (94%), mp. 115-116℃. 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}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.37 (s, methylene H), 7.01 (m, 1H), 7.22 (m, 7H), 7.49 (d, 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 $C_{14}H_{12}N_2$ C: 80.74, H: 5.81, N: 13.45; Found C: 80.66, H: 5.84, N: 13.50.
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A Substituent Effect on the Palladium(II) Catalyzed [3,3]-Sigmatropic Rearrangement of Allylic Esters

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[3,3]-Sigmatropic rearrangements which are represented by Cope[1] and Claisen[2] rearrangements have been applied for pivotal steps in the syntheses of complex molecules. By taking advantage of the stereospecificity and peculiarity of those synthetic methodologies, we recently completed the total syntheses of natural products, (+)-costunolide, dihydroreynosin and dihydrosantamarine, *via* tandem Cope-Claisen rearrangement.[3] In spite of the usefulness of [3,3]-sigmatropic rearrangements in organic synthesis, the required high reaction temperature could be a major drawback for most [3,3]-sigmatropic rearrangements except Ireland-Claisen type[4]. For example, Cope rearrangement usually occurs at higher than 150℃ so that its applicability has been restricted to thermally stable precursors.[5] One reasonable way to circumvent this problem might be the use of catalytic pathway and various catalysts[6], which make [3,3]-sigmatropic rearrangements undergo under mild conditions, have been developed. However, only few of systematic studies[7] have been executed to elucidate the catalytic pathway and much of the reaction mechanism for [3,3]-sigmatropic rearrangements has not been cleared thus far. Allylic ester rearrangement[8], one of