# A New and Facile Synthesis of 1*H*-Indazoles

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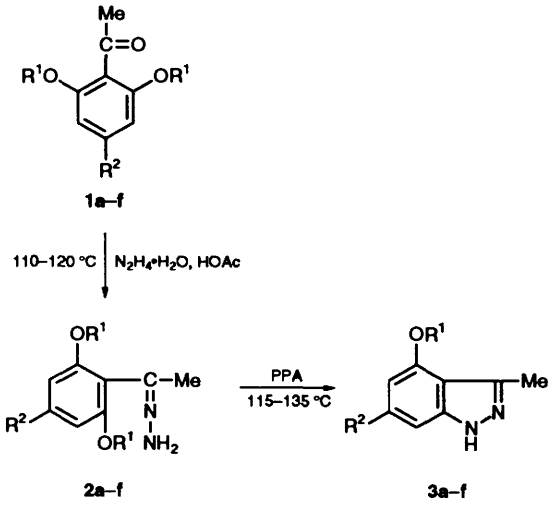
A new and convenient procedure is described for the synthesis of 1*H*-indazoles by cyclization of 2,6-dialkoxyacetophenone hydrazones in the presence of polyphosphoric acid (PPA).

Of the three classical methods for the preparation of 1*H*-indazoles the most frequently used is the diazotization of suitably substituted anilines bearing a hydrocarbon group at the *ortho*-position.[1] A similar reaction occurs when *N*-nitroso-2-methylanilines are heated in the presence of sodium carbonate,[2] and treatment of *o*-chloro-aromatic ketones with a nitro substituent *para* to the chloro substituent with arylhydrazines also gives 1-aryl-1*H*-indazoles.[3] These methods have several limitations as regards the reaction conditions; therefore, several improved syntheses[4-10] have been proposed or developed. However, as far as we know, an efficient synthesis of 1*H*- indazoles in reasonable yield has not yet been reported. We describe here a facile one-pot synthesis of 1*H*-indazoles in high yield.




| 1–3 | $R^1$ | $R^2$ |
|---|---|---|
| **a** | H | H |
| **b** | Me | H |
| **c** | Et | H |
| **d** | Pr | H |
| **e** | Bu | H |
| **f** | Me | OMe |

Treatment of 2,6-dialkoxy (or hydroxy) acetophenones **1a–f** with hydrazine hydrate in the presence of HOAc at 110–120 °C results in hydrazones **2a–f**. After cooling, without isolation of **2a–f**, the addition of PPA followed by stirring at 110–135 °C for about 20 min, gives 3-methyl-4-alkoxy(or hydroxy)-1*H*-indazoles **3a–f**† as the final products.

Application of this method to 2-methoxy-4,6-dimethylacetophenone **1g**, gives 3,4,6-trimethyl-1*H*-indazole **3g**.

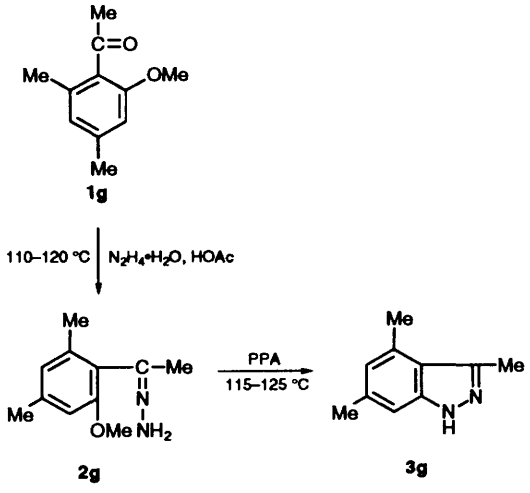
In summary, this new procedure offers several advantages: the easy availability of the reagents, reasonable yield, short reaction time and convenience.

† As 3-methyl-1*H*-indazol-4-ol is very soluble in water it could not easily be extracted from water and was therefore acetylated with acetic anhydride to give 4-acetoxy-3-methyl-1*H*-indazole.

**Table 1** Synthetic conditions, yields and m.p.s for compounds **3a–g**

| Compound | *T*/°C | *t*/min | Yield (%)[a] | M.p. (°C)[b] |
|---|---|---|---|---|
| **3a** | 115–125 | 25 | 34 | 206–208 |
| **3b** | 120–130 | 20 | 87 | 128–130 |
| **3c** | 120–135 | 25 | 80 | 130–131 |
| **3d** | 120–135 | 30 | 62 | 100–102 |
| **3e** | 120–130 | 30 | 60 | 64–65 |
| **3f** | 120–135 | 25 | 65 | 166–168 |
| **3g** | 115–125 | 25 | 73 | 206–208 |

[a] Yield of isolated product. [b] Uncorrected.




## Experimental

*4-Acetoxy-3-methyl-*1H*-indazole* **3a**: *Typical Procedure A.*—2,6-Dihydroxyacetophenone **1a** (1.52 g, 10 mmol), 85% hydrazine hydrate (1.20 g, 20 mmol) and HOAc (10 drops) were placed in a flask (50 $cm^3$ volume). The mixture was stirred at 110–120 °C (oil bath heating) and the reaction was monitored by TLC for 15 min. After cooling, PPA (12 g) was added to the reaction mixture, which was then stirred at 115–125 °C for 20 min during which the intermediate **2a** disappeared. After cooling, acetic anhydride (1.2 g, 15 mmol) was added to the reaction mixture, which was stirred at 120 °C for 25 min. After cooling, ice–water was added to the reaction mixture. The product was extracted with EtOAc (3 × 40 $cm^3$) and the combined extracts were washed with water (2 × 20 $cm^3$), dried ($Na_2SO_4$) and evaporated to give a crystalline residue. Chromatography on silica gel using light petroleum (b.p. 60–90 °C) and EtOAc (4:1) as eluent yielded **3a** (0.65 g, 34%); m.p. 206–208 °C.

**Table 2** Elemental analyses and spectroscopic characterizations for **3a–g**

| Compound | Molecular formula | Found[a] (Required) (%) C | H | N | $\nu_{max}$/cm [b] | *m/z*[c] | $\delta_H$[$CDCl_3$; $(CH_3)_4Si$][d] |
|---|---|---|---|---|---|---|---|
| **3a** | $C_{10}H_{10}N_2O_2$ (190.20) | 63.25 (63.14 | 5.12 5.30 | 14.38 14.73) | 3165, 1760, 1627 1597, 1535, 1204, 1153, 820 | 190 ($M^+$), 175 (b), 147, 119 | 2.64 (3 H, s, $OCCH_3$), 2.75 (3 H, s, $CH_3$), 5.85 (1 H, br, NH), 6.92–7.70 (3 H, m, ArH) |
| **3b** | $C_9H_{10}N_2O$ (162.19) | 66.64 (66.67 | 6.47 6.21 | 17.16 17.28) | 3171, 1623, 1596, 1525, 1354, 1257, 1114, 995, 847 | 162 ($M^+$, b), 147, 131, 119 | 2.80 (3 H, s, $CH_3$), 4.07 (3 H, s, $OCH_3$), 6.60–7.67 (3 H, m, ArH), 8.56 (1 H, br, NH) |
| **3c** | $C_{10}H_{12}N_2O$ (176.22) | 68.06 (68.15 | 7.07 6.81 | 15.97 15.90) | 3166, 1622, 1597, 1525, 1373, 1261, 1122, 774 | 176 ($M^+$), 148 (b), 131, 119 | 1.64 (3 H, t, $OCH_2CH_3$), 2.95 (3 H, s, $CH_3$), 4.52 (2 H, q, $OCH_2CH_3$), 6.94–8.00 (3 H, m, ArH), 9.60 (1 H, br, NH) |
| **3d** | $C_{11}H_{14}N_2O$ (190.24) | 69.61 (69.64 | 7.00 7.42 | 14.60 14.73) | 3166, 1623, 1596, 1524, 1373, 1261, 1100, 768 | 190 ($M^+$), 148 (b), 147, 119 | 1.07 (3 H, t, $OCH_2CH_2CH_3$), 1.84 (2 H, m, $OCH_2CH_2CH_3$), 2.62 (3 H, s, $CH_3$), 3.87 (2 H, t, $OCH_2CH_2CH_3$), 6.02–7.04 (3 H, m, ArH), 9.15 (1 H, br, NH) |
| **3e** | $C_{12}H_{16}N_2O$ (204.27) | 70.29 (70.55 | 7.66 7.90 | 13.63 13.72) | 3167, 1622, 1597, 1524, 1373, 1263, 1110, 772 | 204 ($M^+$), 176, 148 (b), 147, 119 | 0.80–2.15 (7 H, m, $OCH_2CH_2CH_2CH_3$), 2.65 (3 H, s, $CH_3$), 3.90 (2 H, t, $OCH_2CH_2CH_2CH_3$), 6.06–7.05 (3 H, m, ArH), 9.50 (1 H, br, NH) |
| **3f** | $C_{10}H_{12}N_2O_2$ (192.22) | 62.52 (62.28 | 6.08 6.29 | 14.36 14.57) | 3182, 1636, 1602, 1531, 1392, 1202, 1144, 804 | 192 ($M^+$, b) 117, 149, 134, 119 | 2.87 (3 H, s, $CH_3$), 4.15 (3 H, m, s, $OCH_3$) 4.24 (3 H, s, $OCH_3$), 6.67–6.94 (2 H, m, ArH), 7.92 (1 H, s, NH) |
| **3g** | $C_{10}H_{12}N_2$ (160.22) | 74.94 (74.96 | 7.76 7.55 | 17.85 17.49) | 3176, 1622, 1597, 1445, 1344, 1231, 990, 833 | 160 ($M^+$, b) 159, 145, 115 | 2.64 (3 H, s, $CH_3$), 2.88 (3 H, s, Ar–$CH_3$), 2.94 (3 H, s, Ar–$CH_3$), 7.45 (2 H, d, ArH), 7.87 (1 H, s, NH) |

[a] Analysed on a Perkin-Elmer 240C element analytical meter. [b] Recorded on a Nicolet-170 SX-FT-IR spectrophotometer (KBr). [c] Recorded on a VG-ZAB-HS mass spectrometer (EI). [d] Recorded on a JEOL PMX-60SI spectrometer (60 MHz).

*4-Methoxy-3-methyl-1H-indazole* **3b**: *Typical Procedure B.*— A mixture of 2,6-dimethoxyacetophenone **1b** (0.90 g, 5 mmol), 85% hydrazine hydrate (0.60 g, 10 mmol) and HOAc (10 drops) was stirred at 110–120 °C, and monitored by TLC. After 25 min the intermediate **1b** had disappeared. After cooling, PPA (10 g) was added to the mixture, which was then stirred at 120–135 °C for 20 min, during which time the intermediate **2b** disappeared. After cooling, ice–water was added to the mixture. The product was extracted with EtOAc (3 × 40 $cm^3$), and the combined extracts were washed with water, dried ($Na_2SO_4$) and evaporated to give a brown crystalline crude product which was purified as above to give white needles of product **3b**; yield (0.71 g, 87%); m.p. 128–130 °C. Compounds **3c–g** were obtained by a similar procedure as B from **1c–g**.

Compounds **3a–g** were fully characterized by IR, $^1H$ NMR, MS and elemental analysis, the data being listed in Tables 1 and 2.

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