A Convenient Synthesis of Indazoles

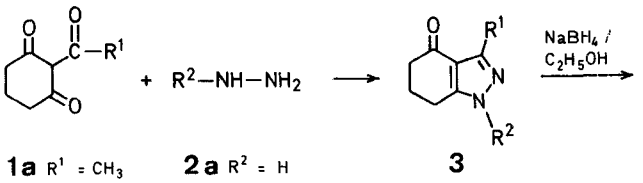
Piero DALLA CROCE, Concetta LA ROSA*

Istituto di Chimica Industriale dell'Università e Centro C.N.R., Via Golgi 19, I-20133 Milano, Italy

Among the many synthetic routes leading to the indazole system[1], the most direct is based on the reaction of cyclohexanone enamines with diazo compounds[2], followed by aromatization of the intermediate tetrahydro derivatives[2,3]. However, the following considerations limit the practical utility of this synthesis:

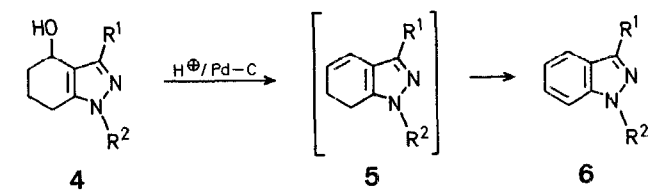
- only activated diazo derivatives may be used, such as diazoketones or diazoesters;
- extreme reaction conditions are required for dehydrogenation of the tetrahydroindazole intermediate (palladium-on-carbon in decalin at 200 °C for 12 h);
- overall yields are low.

In search of a mild method for the dehydrogenation of the tetrahydroindazole intermediate, we reasoned that a dihydroindazole intermediate (i.e. a cyclohexadiene moiety) might undergo the aromatization reaction much more easily than the corresponding cyclohexene derivative normally formed in the reported[2,3] synthesis. Accordingly, we investigated the following reaction sequence for the synthesis of the title compounds.



1a $R^1 = CH_3$ **2a** $R^2 = H$
b $R^1 = C_6H_5$ **b** $R^2 = C_6H_5$
c $R^1 = COOC_2H_5$

3



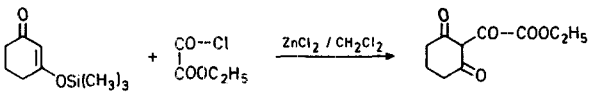
4 5 6

Hydrazines **2** selectively react with the acyl carbonyl group of 2-acylcyclohexane-1,3-diones **1**, giving rise to tetrahydroindazolinones **3** which are readily reduced to hydroxy derivatives **4** with ethanolic sodium borohydride. The subsequent dehydration/aromatization reaction, the most significant step in this indazole synthesis, is carried out by heating **4** at 100 °C in a dioxan solution of *p*-toluenesulfonic acid in the presence of palladium-on-carbon to give high yields of indazole derivatives **6** (Table).

The experimental conditions employed are much simpler than those in the previous synthesis, reflecting the greater tendency of the intermediate cyclohexadiene system **5** to aromatize. With a view toward practical application, the reaction **4** to **6** is also run using Raney-nickel in various solvents (dioxan, ethanol, toluene) and in the presence of hydrogen acceptors (maleic acid, styrene): in all cases the reaction gave results comparable to those reported above. The structure of the intermediates and final products were confirmed by analytical and spectroscopic data.

2-Acetyl- and 2-benzoylcyclohexane-1,3-diones (**1a, b**) are prepared according to Ref.[11].

2-Ethyloxalylcyclohexane-1,3-dione (1c):



1c

To a stirred suspension of anhydrous zinc chloride (1.36 g, 0.01 mol) in dichloromethane (25 ml) and ether (1 ml) cooled to 0 °C is added ethyl oxalyl chloride (1.37 g, 0.01 mol) under nitrogen, followed shortly by addition of 3-oxo-1-trimethylsilyloxycyclohexene[12] (1.84 g, 0.01 mol). The mixture is stirred at 0 °C for 1 h, then allowed to warm to room temperature, and quenched by addition of water (10 ml). The layers are separated, the aqueous layer is extracted with dichloromethane (3 × 20 ml). The combined organic layers are washed with saturated sodium hydrogen carbonate solution (2 × 20 ml), dried with sodium sulfate, and evaporated. Distillation of the residue affords the pure product **1c**; yield: 1.1 g (52%); b.p. 120 °C/0.5 torr.

$C_{10}H_{12}O_5$	calc.	C 56.60	H 5.65
(212.2)	found	56.42	5.61

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.43 (s, 3H); 2.0–2.8 (m, 6H); 4.35 (q, 2H); 12.2 ppm (s, 1H).

4-Oxo-1,5,6,7-tetrahydroindazoles 3; General Procedure:
Hydrazine or phenylhydrazine **2** (0.01 mol) is added to a cooled (0–5 °C) stirred solution of **1** (0.01 mol) in ethanol (25 ml). The mixture is left at room temperature for 4 h and the solvent evaporated. The crude product is purified by recrystallization.

4-Hydroxy-4,5,6,7-tetrahydroindazoles 4; General Procedure:
To a stirred suspension of sodium borohydride (0.38 g, 0.01 mol) in ethanol (25 ml) is added **3** (0.01 mol) and the mixture is heated to 40 °C for 4 h. The solvent is evaporated and the residue is partitioned between chloroform (25 ml) and 10% aqueous acetic acid (20 ml). The organic layer is separated, washed with water (20 ml), and dried with sodium sulfate. After evaporation of the solvent, the residue is recrystallized.

Indazoles 6; General Procedure:
A mixture of **4** (0.01 mol), 10% palladium-on-charcoal (100 mg) and *p*-toluenesulfonic acid (100 mg) in dioxan (25 ml) is stirred at 100 °C for 8 h. The suspension is filtered to remove the catalyst and the solution evaporated. The residue is taken up in chloroform (25 ml), washed with 5% aqueous sodium hydrogen carbonate (20 ml), and the organic layer separated. Evaporation of solvent leaves the crude product which is purified by recrystallization.

Table. Tetrahydroindazolinones **3**, Hydroxytetrahydroindazoles **4**, and Indazoles **6** prepared

Product	Yield [%]	m.p. [°C][a] (solvent)	Molecular formula[b] or Lit. m.p. [°C]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3aa	90	152–154° (C_2H_5OAc)	155°[5]	–	–
3ba	95	185–187° (C_2H_5OAc)	187°[4]	–	–
3bb	85	158–160° (C_2H_5OH)	157°[6]	–	–
3ca	72	100–102° (isopropanol)	$C_{10}H_{12}N_2O_3$ (208.2)	3200 (NH)	1.4 (t, 3H, CH_3); 2.0–3.1 (m, 6H, CH_2); 4.4 (q, 2H, CH_2); 8.2 (s, 1H, NH)
3cb	75	118–120° (C_2H_5OH)	$C_{16}H_{16}N_2O_3$ (284.3)	–	1.4 (t, 3H, CH_3); 2.0–3.1 (m, 6H, CH_2); 4.4 (q, 2H, CH_2); 7.0–7.8 (m, 5H_{arom})
4aa	80	158–160° (isopropanol)	$C_8H_{12}N_2O$ (152.2)	3150–3200 (NH, OH)	1.6–2.8 (m, 6H, CH_2); 2.3 (s, 3H, CH_3); 3.4 (m, 1H, OH); 3.7 (t, 1H, CH)
4ba	86	208–210° (C_2H_5OH)	$C_{13}H_{14}N_2O$ (214.3)	3200–3400 (NH,OH)	1.5–2.8 (m, 6H, CH_2); 4.6–5.0 (m, 3H, NH,OH,CH); 7.2–8.0 (m, 5H_{arom})
4bb	95	140–142° (C_2H_5OH)	$C_{19}H_{20}N_2O$ (292.4)	3500 (OH)	1.8–2.8 (m, 7H, CH_2, OH); 5.1 (m, 1H, CH); 7.2–8.0 (m, 10H_{arom})
4ca	82	122–123° (isopropanol)	$C_{10}H_{14}N_2O_3$ (210.2)	3200–3300 (NH,OH)	1.4 (t, 3H, CH_3); 1.5–2.8 (m, 6H, CH_2); 4.3 (q, 2H, CH_2); 4.5–5.0 (m, 3H, NH,OH,CH)
4cb	85	78–80° (C_2H_5OH)	$C_{16}H_{18}N_2O_3$ (286.3)	3400 (OH)	1.4 (t, 3H, CH_3); 1.6–2.8 (m, 6H, CH_2); 4.3 (q, 2H, CH_2); 4.8 (t, 1H, CH); 5.7 (s, 1H, OH); 7.2–8.0 (m, 5H_{arom})
6aa	85	110–112° (hexane)	113°[8]	–	–
6ba	90	106–107° (hexane)	107–108°[7]	–	–
6bb	89	98–100° (isopropanol)	100–101°[9]	–	–
6ca	80	132–134° (isopropanol)	134–135°[2]	–	–
6cb	85	112–114° (C_2H_5OH)	114–115°[10]	–	–

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.42, H ±0.24, N ±0.32

Received: March 27, 1984

[1] R.C. Elderfield, in: *Heterocyclic Compounds*, Vol. 5, R.C. Elderfield, Ed., John Wiley & Sons, New York, 1957, pp. 162–193.
[2] F. Piozzi, A. Umani-Ronchi, L. Merlini, *Gazz. Chim. Ital.* **95**, 814 (1965).
[3] J.P. Burnett, C. Ainsworth, *J. Org. Chem.* **23**, 1382 (1958).
[4] H.J. Teuber, R. Braun, *Chem. Ber.* **100**, 1353 (1967).
[5] A.A. Akhrem, F.A. Lakhvich, *Khim. Dikarbonil'nykh Soedin., Tezisy Dokl. Vses. Konf.* 4th., 1975 (Pub. 1976) 11–12; *C.A.* **87**, 68119 (1977).
[6] W. Sucrow, M. Slopianka, C. Mentzel, *Chem. Ber.* **106**, 745 (1973).
[7] *Beilstein* **23**, 299.
[8] *Beilstein* **23**, 141.
[9] W. Borsche, W. Scriba, *Liebigs Ann. Chem.* **540**, 83 (1939).
[10] W.A.F. Gladstone, R.O.C. Norman, *J. Chem. Soc.* [C] **1966**, 1527.
[11] A.A. Akhrem et al., *Synthesis* **1978**, 925.
[12] S. Torkelson, C. Ainsworth, *Synthesis* **1976**, 722.