Short Communications

New Syntheses of Indazole and 2-Substituted Indazoles

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The chemistry of indazole and its derivatives has been reviewed by Behr.[1] Popular synthetic methods include the ring closure of *ortho* disubstituted benzene derivatives.

We have lately been interested in the reactions of *ortho* substituted nitroarenes.[2] One such compound, *o*-nitrobenzonitrile seemed to be a possible starting material for the synthesis of indazole by a reductive cyclisation.

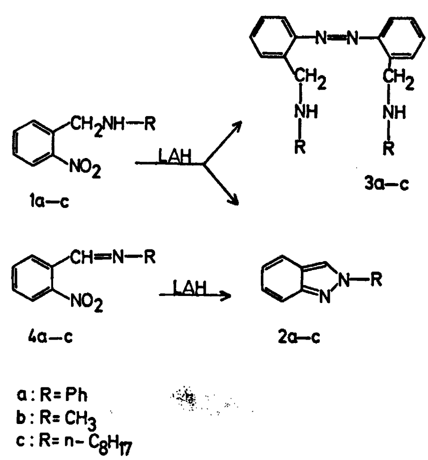
Both nitro groups and cyano groups may be reduced by a variety of reagents, *e.g.* metals or complex metal hydrides. A stepwise reduction of both the nitro group and cyano group might give intermediates able to cyclise to indazole or one of its precursors. Reduction by complex metal hydrides was judged to be the more convenient method.

By reduction of *o*-nitrobenzonitrile with lithium aluminium hydride (LAH), indazole was indeed formed in *ca.* 40 % yield. This yield was obtained when the reduction was performed in refluxing diethyl ether or tetrahydrofuran. Reductions at lower temperatures, down to − 50 °C, gave less indazole and increased yields of by-products. Sodium borohydride reduction of *o*-nitrobenzonitrile did not give indazole.

Catalytic hydrogenation of cyano groups usually demands elevated pressure,[3] and hydrogenation (1 atm., Pd/C) of *o*-nitrobenzonitrile gave only *o*-aminobenzonitrile as product.

o-Aminobenzonitrile did not give indazole on reaction with butyl lithium or LAH. This indicated that the formation of indazole from *o*-nitrobenzonitrile did not proceed *via* this compound.

In an attempt to synthesise 2-substituted indazoles and also to obtain information on the reaction path of the reduction of *o*-nitrobenzonitrile, LAH reduction of *N*-substituted *o*-nitrobenzylamines (*i.e. 1a, 1b* and *1c*) and of *N*-substituted *o*-nitrobenzylidenamines (*i.e. 4a, 4b* and *4c*) was studied. Moderate (50 %) or poor yields have been reported on tin reductions of *N*-aryl-*o*-nitrobenzylamines, the yields depending on the substituents in the *N*-aryl ring.[1]



LAH reductions of three *N*-substituted *o*-nitrobenzylamines (*1a, 1b* and *1c*, made from *o*-nitrobenzyl chloride and the corresponding amines) gave varying results. The aniline derivatives (*1a*) gave a low yield (31 %) of 2-phenylindazole (*2a*) together with *o,o'*-di-(*N*-phenylaminomethyl)azobenzene (*3a*) (37 %).

N-Methyl-*o*-nitrobenzylamine (*1b*) and *N*-octyl-*o*-nitrobenzylamine (*1c*) did not give any 2-alkylindazoles. The only isolated substance was *o,o'*-di-(*N*-methylaminomethyl)azobenzene (*3b*) (63 %) from the reduction of *1b*. These attempts to synthesis 2-substituted indazoles from the corresponding *N*-substituted *o*-nitrobenzylamines thus met with only limited success.

The LAH reduction of the three *N*-substituted *o*-nitrobenzylidenamines (*4a, 4b* and *4c*, made from *o*-nitrobenzaldehyde and the corresponding amines)[4] gave rather better results. The products from all three imines were the corresponding 2-substituted indazoles: 2-phenylindazole (*2a*) (74 %), 2-methylindazole (*2b*) (71 %) and 2-octylindazole (*2c*) (74 %).

The indazoles *2a*[5–7] and *2b*[8,9], were identified by comparison with authentic samples. Compound *2c* was identified from its spectral properties which were closely related to those of *2b*. No 1-substituted indazoles were found from these reactions, however, low yields of these cannot be excluded.

An attempt to obtain indazole itself by LAH reduction of *o*-nitrobenzylidenamine (in an equilibrium mixture with *o*-nitrobenzaldehyde and ammonia) was unsuccessful. Neither did catalytic hydrogenation of *o*-nitrobenzylidenaniline give any 2-phenylindazole.

The poor results from the reduction of the *o*-nitrobenzylamines *1* and the ready formation of the indazoles *2* from the *o*-nitrobenzylidenamines *4* may indicate an imine to be an important intermediate in the reductive cyclisation of *o*-nitrobenzonitrile to indazole.

The described reactions offer new syntheses of indazole and 2-substituted indazoles from readily available starting materials.[4] It may also be possible to use such reactions for the formation of further substituted indazoles.

Experimental. The general instrumentation has been described.[2] NMR signals are given in δ values. The products described were identified by comparison with authentic samples or by their spectroscopic properties.

Syntheses of 2-substituted indazoles (2). The imine *4* was dissolved in diethyl ether (200 ml) and dripped into a refluxing suspension of LAH (2 g) in diethyl ether (200 ml) during 40 min. After 1 h continued reflux, the product was obtained by hydrolysis of the reduction mixture followed by chromatography (dry column, silica gel, chloroform). 2-Phenylindazole (*2a*) (74 % yield) had m.p. 82 – 82.5 °C (lit.[5] 83 – 84 °C) and gave a picrate with m.p. 91 °C (lit.[6,7] 93 – 94 °C). 2-Methylindazole (*2b*) (71 % yield) had m.p. 53 °C (lit.[8] 56 °C). UV (EtOH):[9] λ_{max} 268 nm, ε_{max} 590 m^2 mol^{-1}; λ_{max} 288, ε_{max} 550. IR: 3100, 3050, 2950, 1630, 1520, 1390, 1300, 1160;, 1010, 910, 820, 790, 760 cm^{-1}. NMR ($CDCl_3$): δ 3.84 (3 H, s), 6.4 – 7.8 (5 H, m). 2-Octylindazole (*2c*) (70 % yield). UV (EtOH): λ_{max} 268 nm, ε_{max} 700 m^2 mol^{-1}; λ_{max} 286, ε_{max} 660. IR: 3050, 2950, 1660, 1620, 1500, 1460, 1150, 750 cm^{-1}. NMR ($CDCl_3$): δ 0.85 (3 H, t), 1.0 – 1.3 (10 H), 1.9 (2 H m), 4.2 (2 H, t), 6.8 – 7.8 (5 H, m), MS: *m/e* 230 (58 %, $C_{15}H_{22}N$).

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Adenylyl Cyclase in Isolated Plasma Membranes of Granulation Tissue

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In an earlier paper[1] we have reported on the activities of 5′-nucleotidase (EC 3.1.3.5), Na^+,-K^+-activated Mg^{2+}-dependent adenosine triphosphatase (EC 3.6.1.3) and leucine-β-naphthylamidase (EC 3.4.11.1) in the plasma membranes isolated from experimental granulation tissue and then incubated in various conditions. The purpose of this note is to extend the observations to adenylyl cyclase (EC 4.6.1.1).

The purification of the adenylyl cyclase activity in the plasma membranes was of the same magnitude (18 ×) as calculated from the activities of 5′-nucleotidase, Na^+,K^+-activated Mg^{2+}-dependent adenosine triphosphatase and leucine-β-naphthylamidase[2] and slightly higher in the preparations from mature (3 week) granuloma than from proliferating (1 week) tissue (Table 1). Adenylyl cyclase is relatively insoluble;[3] only about 10 % of the total activity could be solubilized from the membranes with Lubrol WX.[4] This is in agreement with the earlier observations.

Cyclic AMP (10^{-3} – 10^{-6} M) stimulated by 15 – 30 % the activity of 5′-nucleotidase[5] of the plasma membrane both in incubated slices and isolated membrane preparations. Neuraminidase (EC 3.2.1.18) (12.5 U/sample) inhibited the activity of adenylyl cyclase in plasma membranes by 20 – 30 %, whereas hyaluronidase (EC 4.2.99.1) and collagenase (EC 3.4.4.19) were without any effect. Serotonin stimulated the

Table 1. Activity of adenylyl cyclase in various preparations of homogenized granulation tissue. Activities are expressed in (µmol cAMP formed)/(mg protein/min) and the figures are means of duplicates.

Subcellular fraction	Age of granuloma 7 d	21 d
Whole homogenate	0.6	–
7000 *g* supernatant	0.4	4.6
7000 *g* sediment	1.8	–
< 20 % sucrose	0.7	1.1
20 – 28 % sucrose [a]	3.8	8.1
28 – 38 % sucrose [b]	11.0	13.3

[a] "Light" plasma membranes. [b] "Heavy" plasma membranes (the bulk).