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Synthesis and reactions of 1-aryl-3-formyl-4,6-dinitro-1*H*-indazoles

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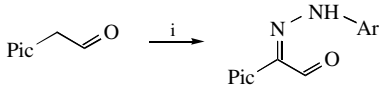
The title compounds were prepared by the reactions of picrylacetaldehyde with aryldiazonium salts followed by the intramolecular cyclization of the resulting picrylglyoxal monoarylhydrazones, and the regiospecific substitution for the nitro group at the 4-position under the action of anionic N-, O- and S-nucleophiles was found.

Previously,[1] we reported on the synthesis of picrylacetaldehyde from 2,4,6-trinitrotoluene. In the studies of picrylacetaldehyde as a multipurpose synthon, we found that it can serve as a precursor of various heterocyclic compounds with functional substituents. In particular, we developed a method[2] for the synthesis of 6-nitrobenzo[*d*]isoxazoles with different substituents at the 3- and 4-positions.

Here we report a convenient procedure for the preparation of previously unknown 1-aryl-3-formyl-4,6-dinitro-1*H*-indazoles from picrylacetaldehyde and the synthesis of 1,3,4-substituted 6-nitroindazoles on this basis.

At the first stage, to obtain dinitroindazoles, picrylacetaldehyde reacted with aryldiazonium salts to form picrylglyoxal monohydrazones **1a–c** (Scheme 1).



picrylacetaldehyde **1a–c**

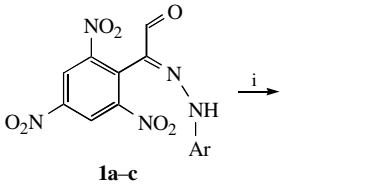
Pic = 2,4,6-$(NO_2)_3C_6H_2$

a Ar = Ph
b Ar = *p*-ClC_6H_4
c Ar = *p*-$MeOC_6H_4$

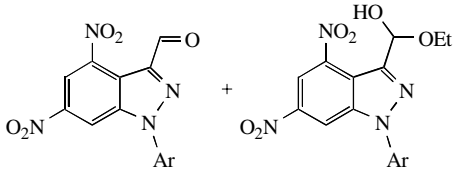
Scheme 1 *Reagents and conditions*: i, $ArNH_2$ (1 equiv.), H_2O–HCl, $NaNO_2$ (1 equiv.), EtOH, AcONa, 5–10 °C, 1 h.

1-Aryl-3-formyl-4,6-dinitro-1*H*-indazoles **2a–c** (Scheme 2) are formed on the treatment of hydrazones **1a–c** with alkalies or alkali metal carbonates. The best results were obtained with K_2CO_3 in EtOH at room temperature. Hydrazones **1a–c** undergo cyclization due to intramolecular nucleophilic substitution for the nitro group (Scheme 2). Hydrazones **1a–c** were used without additional purification because compounds **2a–c** were formed to a degree even in the course of their preparation.

A characteristic property of formyldinitroindazoles **2** with no electron-donor groups at the N-aryl substituent is the formation of stable hemiacetals **3a**,**b**, which are partially formed even in the course of the synthesis of compounds **2** (Scheme 2). These latter can be completely converted into hemiacetals **3a**,**b** on boiling in ethanol for 30 min. Crystalline hemiacetal **3a** eliminates an alcohol molecule on heating in air (80 °C, 8 h) to regenerate formyldinitroindazole **2a**.



1a–c



2a–c **3a**,**b**

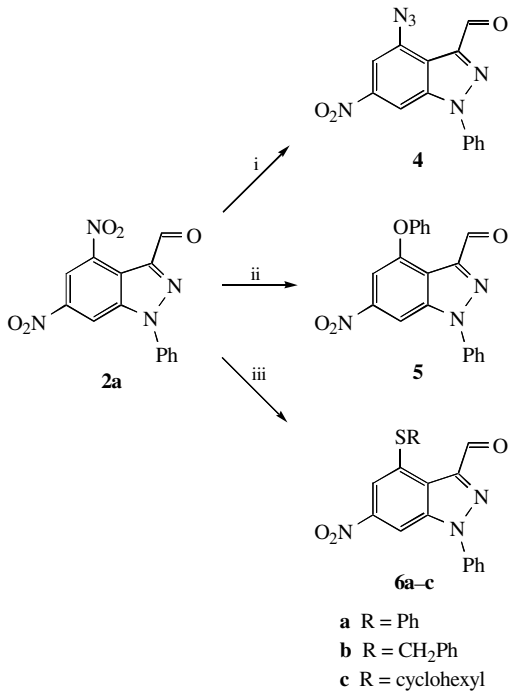
a Ar = Ph
b Ar = *p*-ClC_6H_4
c Ar = *p*-$MeOC_6H_4$

Scheme 2 *Reagents and conditions:* i, K_2CO_3 (1 equiv.), EtOH, 20 °C, 24 h.

The reactions of formyldinitroindazoles were studied using 3-formyl-4,6-dinitro-1-phenyl-1*H*-indazole **2a** as an example. We found that the test compound reacts with N-, O- and S-nucleophiles (in DMF or *N*-methylpyrrolidone solutions) so that substitution for only the nitro group at the 4-position takes place to give previously unknown 4-substituted 3-formyl-6-nitro-1-phenyl-1*H*-indazoles **4–6** as sole products (Scheme 3). Phenol and thiols were used as nucleophiles in the presence of solid K_2CO_3 (in an equimolar amount), as well as NaN_3. The reaction with NaN_3 was performed at room temperature, whereas the reactions with phenol and thiols were performed at 80 and 60 °C, respectively, to the complete conversion of parent indazole **2a**. Note that the results were identical in the reactions of aldehyde **2a** and its hemiacetal **3a**.

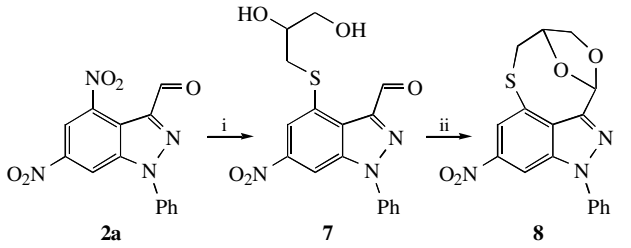
In addition to ^1H and ^{13}C NMR data (including NOE), the direction of substitution was also supported chemically. Thus, glycol **7** was isolated after the reaction with thioglycerol; this glycol afforded intramolecular cyclic acetal under conditions of catalysis with *p*-toluenesulfonic acid (Scheme 4). This product can be formed only by substitution for the nitro group at the 4-position.

Regiospecific substitution for an *ortho* or *para* nitro group was previously observed in substituted di- and polynitrobenzenes,[3,4] as well as (peri nitro group) in 4,6-dinitrobenzo-



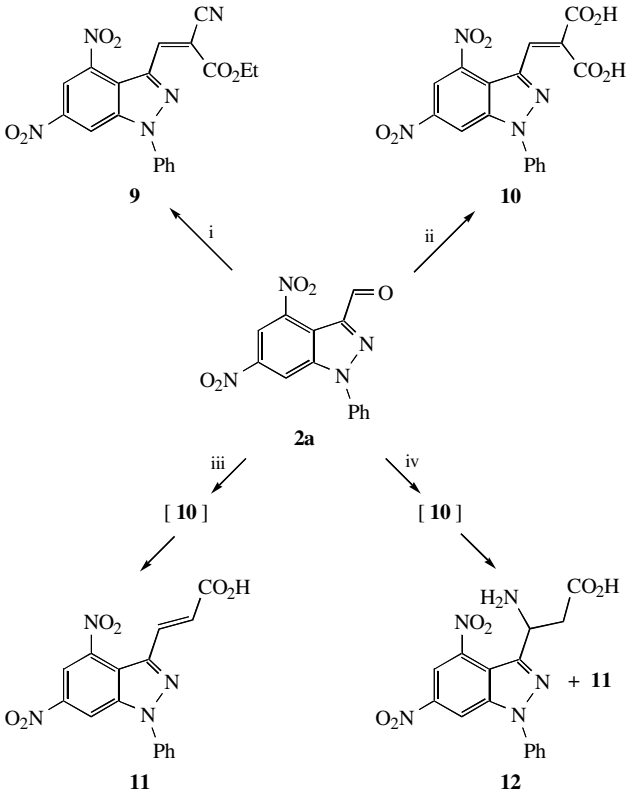
a R = Ph
b R = CH_2Ph
c R = cyclohexyl

Scheme 3 *Reagents and conditions:* i, NaN_3 (1 equiv.), DMF, 20 °C, 24 h; ii, PhOH (1 equiv.), K_2CO_3 (1 equiv.), *N*-methylpyrrolidone, 80 °C, 24 h; iii, RSH (1 equiv.), K_2CO_3 (1 equiv.), *N*-methylpyrrolidone, 60 °C, 24 h.



Scheme 4 *Reagents and conditions*: i, $HSCH_2CH(OH)CH_2OH$ (1 equiv.), K_2CO_3 (1 equiv.), *N*-methylpyrrolidone, 20 °C, 48 h; ii, TosOH (5 mol%), benzene, refluxing for 8 h.

[*b*]thiophene[5] and 4,6-dinitrobenzo[*d*]isoxazole[2] derivatives. The formation of stable hemiacetals **3a**,**b** (Scheme 2) from formyldinitroindazoles **2a**,**b** is indicative of the high electrophilicity of the formyl group. Indeed, indazole **2a** (or its hemiacetal) readily reacts with compounds containing active methylene units. For example, unsaturated compound **9** was formed with cyanoacetic ester (Scheme 5). The reaction of compound **2a** with malonic acid should be particularly noted. In this case, various products were formed depending on reaction conditions (Scheme 5). Methylenemalonic acid derivative **10** was obtained when the reaction was performed in ethanol in the presence of NH_4OAc, whereas acrylic acid derivative **11** was obtained on heating in pyridine with the use of piperidine as a catalyst; that is, dicarboxylic acid **10** underwent decarboxylation under these conditions. If the reaction was performed in acetic acid in the presence of an excess of NH_4OAc (Rodionov reaction conditions[6]), acrylic acid derivative **11** (28% yield) and 3-aminopropionic acid derivative **12** (20% yield, Scheme 5) were formed. We found that under reaction conditions acid **11** did not add ammonia to form amino acid **12**. At the same time, methylenemalonic acid **10** gave a mixture of acids **11** and **12** in 20 and 32% yields, respectively. Thus, the reaction of compound **2a** with malonic acid in the presence of NH_4OAc in acetic acid initially resulted in dicarboxylic acid **10**, which underwent decarboxylation to compound **11** and added ammonia and then underwent decarboxylation to amino acid **12**.



Scheme 5 *Reagents and conditions:* i, $CH_2(CN)CO_2Et$ (1 equiv.), NH_4OAc (10 mol%), AcOH (10 mol%), benzene, 80 °C, 6 h; ii, $CH_2(CO_2H)_2$, NH_4OAc (2 equiv.), EtOH, 78 °C, 5 h; iii, $CH_2(CO_2H)_2$, piperidine (10 mol%), Py, 115 °C, 5 h; iv, NH_4OAc (3 equiv.), AcOH, 118 °C, 10 h.

The structures of the synthesised compounds were supported by ^1H and ^{13}C NMR spectroscopy, mass spectrometry (molecular ions were detected in all cases), IR spectroscopy and elemental analysis.†

Thus, we developed a convenient method for the synthesis of multifunctional compounds, 1-aryl-3-formyl-4,6-dinitro-1*H*-indazoles, and prepared a number of new 1-phenyl-3-R-4-R′-nitroindazoles on this basis.

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† NMR spectra were measured in $[^2H_6]$DMSO on a Bruker AM-300 instrument using TMS as an internal standard.

1a: yield 79%. ^1H NMR, δ: 7.05 (m, 1H, Ph), 7.30 (m, 4H, Ph), 9.21 (s, 2H, Pic), 9.53 (1H, CHO), 11.11 (s, 1H, NH).

1b: yield 66%. ^1H NMR, δ: 7.32 (m, 4H, *p*-ClC_6H_4), 9.21 (s, 2H, Pic), 9.56 (1H, CHO), 11.12 (s, 1H, NH).

1c: yield 71%. ^1H NMR, δ: 3.79 (s, 3H, Me), 6.90, 7.25 (2d, 4H, *p*-$MeOC_6H_4$), 9.20 (s, 2H, Pic), 9.47 (s, 1H, CHO), 11.10 (s, 1H, NH). On heating, the hemiacetals lost an ethanol molecule before melting.

2a: yield 91%, mp 190–191 °C (EtOH). ^1H NMR, δ: 7.71 (m, 3H, Ph), 7.92 (m, 2H, Ph), 8.79, 8.87 (2d, 1H each, 5-H and 7-H, $^4J_{H–H}$ 1.61 Hz), 10.33 (s, 1H, CHO).

2c: yield 82%, mp 210–212 °C (EtOH). ^1H NMR, δ: 3.92 (s, 3H, Me), 7.22, 7.75 (d, 2H each, *p*-$MeOC_6H_4$, $^3J_{H–H}$ 8.85 Hz), 8.76 (s, 2H, 5-H and 7-H), 10.32 (s, 1H, CHO).

3a: yield 96%. ^1H NMR, δ: 1.14 (t, 3H, Me, $^3J_{H–H}$ 6.96 Hz), 3.54, 3.87 (m, 1H each, CH_2), 5.95, 6.69 (d, 1H each, OCH and OH, $^3J_{H–H}$ 9.11 Hz), 7.5–7.9 (m, 5H, Ph), 8.53, 8.77 (d, 1H each, 5-H and 7-H, $^4J_{H–H}$ 1.60 Hz).

3b: yield 86%. ^1H NMR, δ: 1.13 (t, 3H, Me, $^3J_{H–H}$ 6.99 Hz), 3.50, 3.82 (2m, 1H each, CH_2), 5.89, 6.83 (d, 1H each, OCH and OH, $^3J_{H–H}$ 9.32 Hz), 7.68, 7.89 (d, 2H each, *p*-ClC_6H_4, $^3J_{H–H}$ 8.85 Hz), 8.53, 8.80 (d, 1H each, 5-H and 7-H).

4: yield 75%, mp 193–194 °C (decomp.). ^1H NMR, δ: 7.6–7.9 (m, 5H, Ph), 8.01, 8.35 (s, 1H each, 5-H and 7-H), 10.53 (s, 1H, CHO).

5: yield 70%, mp 192–194 °C. ^1H NMR, δ: 7.2–7.4, 7.5–7.8, 7.9 (3m, 11H, OPh, NPh, 5-H), 8.32 (s, 1H, 7-H), 10.53 (s, 1H, CHO).

6a: yield 95%, mp 199–200 °C. ^1H NMR, δ: 7.45 (s, 1H, 5-H), 7.5–7.9 (m, 10H, SPh, NPh), 8.25 (s, 1H, 7-H), 10.43 (s, 1H, CHO).

6b: yield 90%, mp 152–153 °C. ^1H NMR, δ: 4.48 (s, 2H, CH_2), 7.2–7.9 (m, 10H, NPh, CPh), 8.01, 8.24 (d, 1H each, 5-H and 7-H, $^4J_{H–H}$ 1.61 Hz), 10.38 (s, 1H, CHO).

6c: yield 89%, mp 173–175 °C. ^1H NMR, δ: 1.3–1.9, 2.0–2.2 [m, 10H, $(CH_2)_5$], 3.61 (m, 1H, SCH), 7.5–7.9 (m, 5H, Ph), 8.01, 8.30 (d, 1H each, 5-H and 7-H, $^4J_{H–H}$ 1.40 Hz), 10.58 (s, 1H, CHO).

7: yield 62%, oily product. ^1H NMR, δ: 2.9–3.2, 3.3–3.6 (2m, 2H each, SCH_2, OCH_2), 3.80 (m, 1H, OCH), 4.6, 4.9 (br. s, 1H each, OH), 7.5–7.9 (m, 5H, Ph), 8.07, 8.21 (2d, 1H each, 5-H and 7-H, $^4J_{H–H}$ 1.61 Hz), 10.51 (s, 1H, CHO).

8: yield 53%, mp 157–160 °C (decomp.). ^1H NMR, δ: 3.20 (m, 2H, SCH_2), 4.05 (dd), 4.52 (d) (1H each, OCH_2), 4.81 (m, 1H, OCH), 6.32 (s, 1H, OCHO), 7.4–7.8 (m, 5H, Ph), 8.13, 8.39 (2d, 1H each, 5-H and 7-H, $^4J_{H–H}$ 1.61 Hz).

9: yield 46%, mp > 300 °C (decomp.). ^1H NMR, δ: 1.41 (t, 3H, Me, $^3J_{H–H}$ 6.57 Hz), 4.40 (q, 2H, CH_2, $^3J_{H–H}$ 6.57 Hz), 7.6–7.8 (m, 3H, Ph), 7.9–8.1 (m, 2H, Ph), 8.86, 8.92, 8.98 (3s, 1H each, HC=C, 5-H and 7-H).

10: yield 84%, mp > 300 °C (decomp.). ^1H NMR, δ: 7.5–8.0 (m, 5H, Ph), 8.10, 8.83, 9.01 (3s, 1H each, HC=C, 5-H and 7-H), 12.9 (br. s, 2H, OH).

11: yield 44%, mp > 300 °C (decomp.). ^1H NMR, δ: 6.76 (d, 1H, HC=C, $^3J_{H–H}$ 15.26 Hz), 7.5–7.7 (m, 3H, Ph), 7.8–7.9 (m, 2H, Ph), 8.04 (d, 1H, HC=C, $^3J_{H–H}$ 15.26 Hz), 8.78, 8.84 (s, 1H each, 5-H and 7-H), 12.43 (br. s, 1H, OH).

12: yield 20%, mp 217–218 °C. ^1H NMR, δ: 2.9–3.1 (m, 2H, CH_2), 5.76 (dd, 1H, $HCNH_2$), 7.5–7.9 (m, 6H, NH_2, Ph), 8.30 (d, 1H, NH_2), 8.61, 8.79 (d, 1H each, 5-H and 7-H, $^4J_{H–H}$ 1.40 Hz).

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