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SYNTHESIS AND OXIDATION OF 1,3-DIAMINO- AND 1-AMINO-3-AZIDOINDAZOLES

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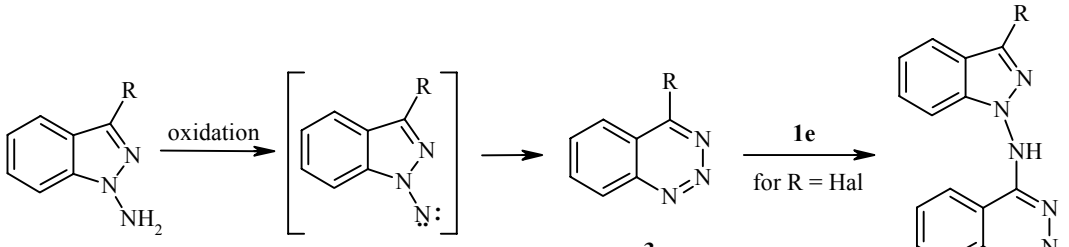
The amination of 3-amino- and 3-azidoindazoles by hydroxylamine-O-sulfonic acid in an alkaline medium yields previously unreported 1,3-diamino- and 1-amino-3-azidoindazoles. These products undergo slow autoxidation in chloroform solution to give 4-aminobenzo-1,2,3-triazine. The action of formic or acetic acid on 3-amino-1-benzylideneaminoindazole leads to recyclization and formation of 3-amino-2-benzylindazole, which is also formed in the catalytic hydrogenation of 1-benzylamino-3-nitro- and 1-benzylideneamino-3-nitroindazoles.

Keywords: 1-amino-3-azidoindazole, 4-aminobenzo-1,2,3-triazine, 3-amino-2-benzylindazole, 1,3-diaminoindazole, autoxidation.

1-Aminoindazole (**1a**) and its 3-methyl, 3-phenyl, and 3-methoxy derivatives **1b-d** are oxidized by lead tetraacetate to give benzo-1,2,3-triazines **3a-d** [1, 2]. This reaction presumably proceeds through the corresponding N-nitrenes **2a-2d**, which are stabilized by ring expansion as discussed in our previous work [3]. 1-Amino-3-haloindazoles **1e** display special behavior [4]. The action of lead tetraacetate on these rather unstable compounds gives complex mixtures of undetermined compounds, while they undergo slow autoxidation in chloroform solution to give 4-(3-haloindazol-1-yl)aminobenzo-1,2,3-triazines **4e**, probably as the result of aminodehalogenation of intermediate 4-halobenzo-1,2,3-triazines **3e** by the action of the starting amine. The reaction is complete in 72-120 h and the yield of **4e** is 16-27%. 1-Amino-3-nitroindazole (**1f**) is unaltered in chloroform solution [5]. Hence, it was of interest to study the behavior of previously unreported 1,3-diamino- (**1g**) and 1-amino-3-azidoindazoles (**1h**).



1a–h **2a–h** **3a–g** **4e**

1-4 a R = H; **b** R = Me; **c** R = Ph; **d** R = OMe; **e** R = Cl, Br, I; **f** R = NO_2; **g** R = NH_2; **h** R = N_3

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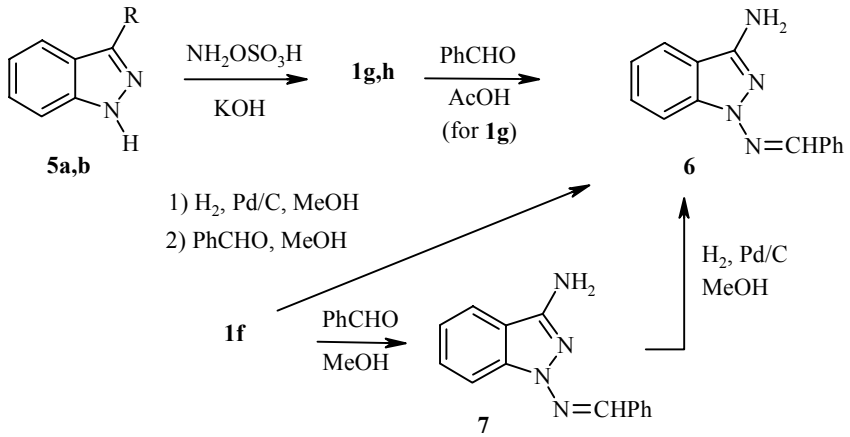
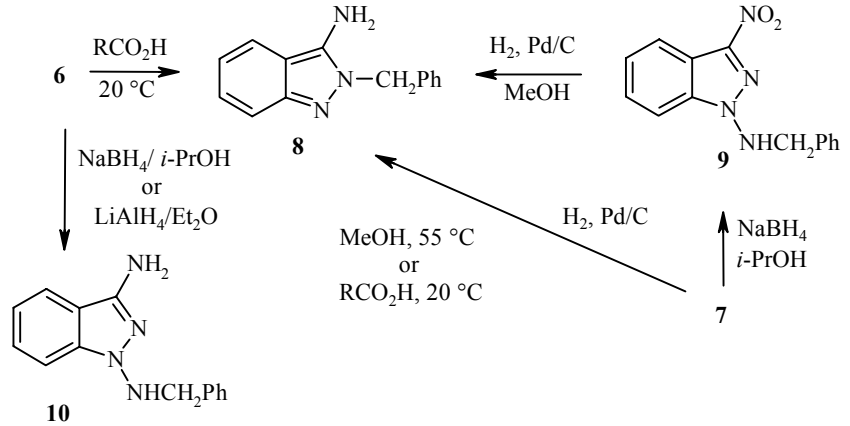
The electrophilic amination of 3-aminoindazole **5a** by hydroxylamino-O-sulfonic acid (HASA) in aqueous alkali led to 1,3-diaminoindazole **1g** in 10% yield. Such a low yield may be attributed both to the difficulty of amination of amine **5a**, probably due to its incomplete conversion to the N-anion, and the difficulty in separating the reaction product from the starting compound, requiring fractional crystallization. The actual yield of diamine **1g** reaches 21% as indicated by the isolation of its benzylidene derivative **6** in this yield upon heating the crude reaction mixture with benzaldehyde in acetic acid at reflux. The structure of **6** was proved by its synthesis through the catalytic hydrogen hydrogenation of 1-benzylideneamino-3-nitroindazole (**7**) in 88% yield described in our previous work [5]. Thus, the N-amino group in diamine **1g** reacts more readily with benzaldehyde than the 3-amino group.



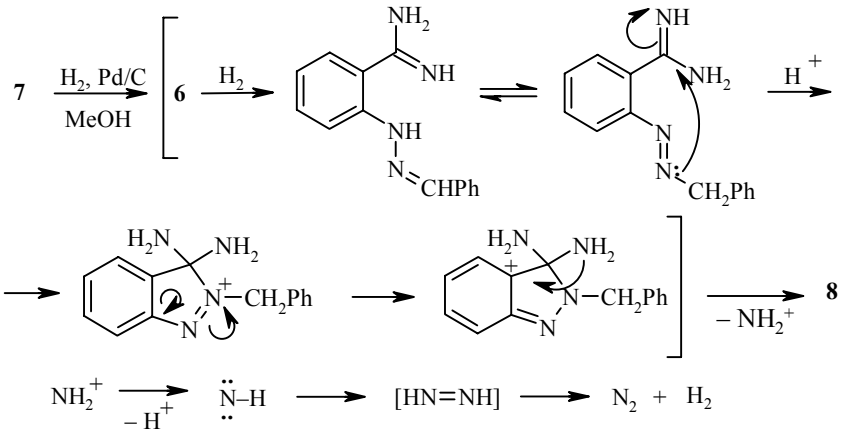
1g, **5a** R = NH_2, **3h**, **5b** R = N_3

We attempted to develop alternative methods for the synthesis of diamine **1g**. The reduction of the nitro group in 1-amino-3-nitroindazole **1f** by excess hydrogen over 2% Pd/C led only to the formation of 3-aminoindazole **5a**. The elimination of the N-amino group probably occurs in intermediate 1,3-diaminoindazole **1g**. Support for this hypothesis lies in the observation that if the reaction is stopped after the absorption of three molar equivalents of hydrogen, diamine **1g** may be isolated in 42% yield as benzylideneamino derivative **6**.

Unfortunately, the selective hydrolysis of azomethine **6** could not be carried out to give diamine **1g**. In contrast to similar compounds [3], the hydrolysis of azomethine **6** in 4% hydrochloric acid does not proceed, while the elimination of the benzylidene group occurs in more acidic media at 20-100°C to give only 3-aminoindazole **5a**.

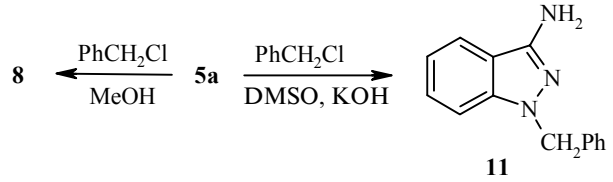


In a study of the hydrolysis of azomethine **6** in formic or acetic acid, previously unreported 3-amino-2-benzylindazole (**8**) was isolated. Benzylindazole **8** is also formed instead of the expected 3-amino-1-benzylaminoindazole (**10**) in the hydrogenation of 1-benzylamino-3-nitroindazole (**9**), which was obtained by the action of sodium borohydride on 1-benzylideneamino-3-nitroindazole (**7**) in 2-propanol. We should note that $NaBH_4$ and $LiAlH_4$ do not reduce the benzylideneamino group in 3-amino-1-benzylideneaminoindazole **6** and, thus, 3-amino-1-benzylaminoindazole **10** could not be prepared. This behavior should be attributed to prior ionization of the 3-amino group to the N-anion, which is inert to subsequent reduction.



Benzylindazole **8** is also formed in 10% yield in the catalytic hydrogenation of 1-benzylideneamino-3-nitroindazole **7** in methanol at room temperature; 3-amino-1-benzylideneaminoindazole **6** is also formed. When the reaction temperature is raised to 55°C, the yield of **8** rises to 75%. The reduction of **7** in formic or acetic acid also leads to an enhanced yield of 3-amino-2-benzylindazole **8** to 45-50%. The formation of **8** appears to recall the recently discovered rearrangement of 1-alkylaminopyrazoles and 1-alkylaminoindazoles to give 1-alkyl-5-aminopyrazoles and 2-alkyl-3-aminoindazoles, respectively [6, 7].

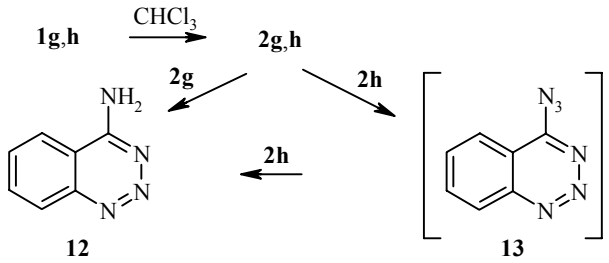
Evidence of the structure of **8** was provided by its independent synthesis involving the benzylation of 3-aminoindazole **5a** using benzyl chloride in methanol. The yield of amine **8** was 22%. It is interesting that only 3-amino-1-benzylindazole (**11**) is formed in 70% yield in the benzylation of **5a** in KOH/DMSO.



11

3-Azido-1-aminoindazole **1h** was obtained in 20% yield by the amination of 3-azidoindazole **5b** with excess HASA analogously to diamine **1g**.

The oxidation of amines **1g** and **1h** in chloroform solution is even slower than for 1-amino-3-haloindazole **1e** and is completed only after 37-30 days. A brown precipitate slowly formed and was identified in both cases as 4-aminobenzo-1,2,3-triazine (**12**) (24-33% yield). As in the case of 1-amino-3-haloindazoles **1e**, this reaction presumably proceeds through the formation of N-nitrenes **2g** and **2h**, which cyclize to give 4-amino- (**12**) and 4-azidobenzo-1,2,3-triazines (**13**). Triazine **13** probably is reduced to amine **12** by reacting with the N-amino group of the starting amine.



The oxidation of amines **1g** and **1h** by lead tetraacetate in methylene chloride leads to the formation of a mixture of unstable compounds, which could not be purified.

Thus, our study has shown that the presence of an electron-donor substituent at $C_{(3)}$ is required for the autoxidation of 1-aminoindazoles in chloroform solution. Further support for this hypothesis lies in the finding that 1-aminoindazole **1a** itself hardly changes upon maintenance in chloroform solution for 10 days.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in vaseline oil. The ^{1}H NMR spectra were registered on a Bruker-250 spectrometer for **1g**,**h**, **8**, **9**, **11**, and **12** and a Unity-300 spectrometer for **6**. The UV and mass spectra of **8** were obtained on a Perkin-Elmer UV-VIS Spectrometer Lambda 10 and Perkin-Elmer Q-Mass 910 spectrometer, respectively. The reaction course and purity of the products were monitored by thin-layer chromatography on alumina plates (Brockmann grade-IV activity, visualization with iodine vapor). The melting points were obtained for samples in sealed capillary tubes and not corrected. The starting compounds were prepared according to the following procedures: 1-amino-3-nitroindazole **1f** [4], 1-benzylidenamino-3-nitroindazole **7** [4], 3-aminoindazole **5a** [8], and 3-azidoindazole **5b** [9].

1,3-Diaminoindazole (1g). A solution of the sodium salt of hydroxylamine-O-sulfonic acid (HASA) in water (10 ml) obtained by the neutralization of HASA (2.5 g, 0.022 mol) with excess $NaHCO_3$ was added to a solution of 3-aminoindazole **5a** (1.33 g, 0.01 mol) and NaOH (2.0 g, 0.05 mol) in a mixture of water (25 ml) and ethanol (5 ml) at 60°C. The reaction mixture was stirred for 20 min and a solution of the sodium salt of HASA in water (5 ml) obtained by the neutralization of HASA (1.25 g, 0.011 mol) with excess $NaHCO_3$. The mixture was stirred for 1 h at 50°C, cooled, and extracted with two 30-ml chloroform portions. Chloroform was distilled off and the residue was subjected to fractional crystallization from octane to give 0.15 g (10%) **1g** as gray needles; mp 118-120°C. IR spectrum in $CDCl_3$, ν, cm^{-1}: 1570, 1620 (ring), 3190, 3287, 3380 (NH_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.9 (2H, br. s, disappears upon deuteration, N–NH_2); 4.9 (2H, br. s, disappears after deuteration, C–NH_2); 7.01 (1H, m, 5-H); 7.37 (2H, m, 6-H, 7-H); 7.46 (1H, m, 4-H). Found, %: C 56.42; H 5.63; N 38.13. $C_7H_8N_4$. Calculated, %: C 56.74; H 5.44; N 37.81.

1-Amino-3-azidoindazole (1h). A solution of HASA (2.5 g, 0.022 mol) in water (10 ml) previously neutralized with dry $NaHCO_3$ was added to a solution of 3-azidoindazole **5b** (1 g, 0.0063 mol) and NaOH (2 g, 0.05 mol) in water (25 ml) at 60°C. The mixture was stirred for 1 h at 55°C, cooled, and extracted with two 30-ml chloroform portions. The chloroform solution was passed through a 22×2.5-cm alumina column using chloroform as the eluent and collecting the fraction with R_f 0.4. Evaporation of chloroform gave 0.22 g (20%) **1g** as colorless needles; mp 112°C (dec., from petroleum ether). IR spectrum, ν, cm^{-1}: 1595, 1620 (ring), 2120 (N_3), 3205, 3320 (NH_3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.1 (2H, br. s, disappears after deuteration, NH_2); 7.09 (1H, m, 5-H); 7.51 (1H, m, 6-H); 7.51 (2H, m, 4-H, 7-H). Found, %: C 47.82; H 3.69; N 48.65. $C_7H_6N_6$. Calculated, %: C 48.27; H 3.47; N 48.25.

3-Amino-1-benzylidenaminoindazole (6). A. A solution of 1-amino-3-nitroindazole **1f** (0.35 g, 2 mmol) in methanol (130 ml) was shaken in a hydrogen atmosphere at 40-45°C in the presence of 2% Pd/C (0.3 g) over 8 h. The catalyst was filtered off. A sample of benzaldehyde (0.5 ml, 5 mmol) was added to the methanolic solution and heated at reflux for 3 h. Two thirds of methanol was distilled off. The residue was evaporated to dryness, dissolved in chloroform (30 ml), and subjected to chromatography on a 30×2.5-cm alumina column with chloroform as the eluent. The fraction with R_f 0.6 was collected. Chloroform was evaporated to give 0.2 g (42%) **6** as yellow-green crystals; mp 127-129°C (1:1 octane–benzene). IR spectrum, ν, cm^{-1}: 1595, 1625 (ring), 1640 (C=N), 3095, 3200, 3310 (NH_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 4.35 (2H, br. s, disappears after deuteration, NH_2); 7.13 (1H, 5-H, dt, $J_{5,6}$ = 7.10); 7.40 (4H, m, 3'-H, 5'-H, 6-H); 7.50 (1H, dt, $J_{4,5}$ = 8.05, 4-H); 7.73 (1H, d, $J_{6,7}$ = 8.42, 7-H); 7.82 (2H, m, 2'-H, 6'-H); 8.54 (1H, s, –CH=). Found, %: C 70.87; H 5.50; N 24.00. $C_{14}H_{12}N_4$. Calculated, %: C 71.16; H 5.11; N 23.71.

B. A solution of 1-benzylideneamino-3-nitroindazole **7** (0.35 g, 1.3 mmol) in methanol (350 ml) was shaken in a hydrogen atmosphere at room temperature in the presence of 2% Pd/C (0.3 g) for 3 h. The catalyst was filtered off. Four fifths of methanol was distilled off. The residue was evaporated to dryness. The yellow-green precipitate was dissolved in chloroform (30 ml) and passed through a 30×2.5-cm alumina column with chloroform as the eluent, collecting two fractions. The first fraction with R_f 0.6 contained 0.27 g (88%) **6** as yellow-green crystals; mp 127-129°C (1:1 octane–benzene). The second fraction with R_f 0.4 gave 0.03 g (10%) 2-benzyl-3-aminoindazole **8** as gray-green crystals, mp 139-140°C (octane).

C. A solution of the sodium salt of HASA in water (10 ml) obtained by the neutralization of HASA (2.5 g, 0.022 mol) with excess $NaHCO_3$ was added to a solution of 3-aminoindazole **5a** (1.33 g, 0.01 mol) and NaOH (2 g, 0.05 mol) in a mixture of water (25 ml) and ethanol (5 ml) at 60°C. The mixture was stirred for 20 min and a solution of the sodium salt of HASA in water (5 ml) obtained by the neutralization of HASA (1.25 g, 0.011 mol) with excess $NaHCO_3$ was added. The mixture was stirred at 50°C for 1 h, cooled, and extracted with two 30-ml chloroform portions. Chloroform was distilled off and benzaldehyde (1 ml, 0.01 mol) and ethanol (10 ml) was added to the residue. The mixture was heated at reflux for 2 h. The solvent was evaporated to dryness. The yellow-green crystalline precipitate formed was dissolved in chloroform (30 ml) and purified on a 30×2.5-cm alumina column with chloroform as the eluent, collecting the fraction with R_f 0.6. Evaporation of chloroform gave 0.5 g (21%) **6** as yellow-green crystals; mp 127-129°C (1:1 octane–benzene).

Hydrolysis of 3-Amino-1-benzylideneaminoindazole (6). A suspension of **6** (0.45 g, 1.9 mmol) in conc. hydrochloric acid (10 ml) was heated at reflux for 15 min. The solution obtained was neutralized with conc. aqueous ammonia to pH 7 and evaporated to dryness. The residue was grinded in ethyl acetate (10 ml). The undissolved NH_4Cl was filtered off. The solution was passed through a 15×2.5-cm alumina column with ethyl acetate as the eluent, collecting the fraction with R_f 0.3. The solvent was evaporated to give 0.25 g (99%) 3-aminoindazole (**5a**) as gray prisms; mp 154°C (benzene).

The hydrolysis was carried out analogously in 12% hydrochloric acid at reflux for 1 h to give 56% **5a**, in 12% hydrochloric acid at room temperature for 24 h to give 38% **5a**, and in 8% hydrochloric acid at room temperature for 120 h to give 19% **5a**.

3-Amino-2-benzylindazole (8). A. A solution of 1-benzylideneamino-3-nitroindazole **7** (0.35 g, 1.3 mmol) in methanol (350 ml) was shaken for 4 h in a hydrogen atmosphere at 55°C in the presence of 2% Pd/C (0.3 g). The catalyst was filtered off and four fifths of the methanol was distilled off. The residue was evaporated to dryness and the oil obtained was dissolved in chloroform (30 ml) and passed through a 30×2.5-cm alumina column with chloroform as the eluent, collecting the fraction with R_f 0.4. Evaporation of chloroform gave 0.225 g (75%) **8** as gray-green crystals; mp 139-140°C (octane). IR spectrum, ν, cm^{-1}: 1560, 1635 (ring), 3170, 3330 (NH_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 3.75 (2H, br. s, disappears after deuteration, NH_2); 5.42 (2H, s, CH_2); 6.83 (1H, m, 5-H); 7.2 (1H, m, 6-H); 7.3 (5H, m, 2'-H, 6'-H); 7.36 (1H, d, 7-H, $^3J_{76}$ = 8.45); 7.47 (1H, d, 4-H, $^3J_{76}$ = 8.87). Mass spectrum, *m/z* (%): 223 (100) (M^+), 207 (5.93) (M^+ - NH_2), 146 (7.97) (M^+ - Ph), 132 (41.68) (M^+ - CH_2Ph), 91 (75.47) (CH_2Ph), 77 (22.48) (Ph). UV spectrum (methanol), λ_{max} (log ε): 260 (4.12), 268 (4.04), 335 (4.39).

B. A solution of 3-amino-1-benzylideneaminoindazole **6** (0.1 g, 0.4 mmol) in conc. formic or acetic acid (10 ml) was left for 24 h at room temperature, neutralized by adding conc. aqueous ammonia to pH 7, and extracted with three 10-ml chloroform portions. The chloroform solution was passed through a 30×1.5-cm alumina column with chloroform as the eluent, collecting the fraction with R_f 0.4. Evaporation of chloroform gave 0.07 g (75%) **8** as light green crystals; mp 139-140°C (octane).

C. A solution of 1-benzylamino-3-nitroindazole **9** (0.134 g, 0.5 mmol) in methanol (50 ml) was shaken for 4 h in a hydrogen atmosphere at 55°C in the presence of 2% Pd/C (0.15 g). The catalyst was filtered off and four fifths of methanol was distilled off. The residue was evaporated to dryness. The oil obtained was dissolved in chloroform (30 ml) and passed through a 30×2.5-cm alumina column with chloroform as the eluent, collecting the fraction with R_f 0.4. Evaporation of chloroform gave 0.08 g (72%) **8** as gray-green crystals; mp 139-140°C (octane).

D. A solution of 3-aminoindazole **5a** (0.133 g, 1 mmol) and benzyl chloride (0.072 ml, 0.62 mmol) in methanol (3 ml) was heated at reflux for 6 h. The solvent was evaporated to dryness. The residue was suspended in water (5 ml) and extracted with three 3-ml chloroform portions. The chloroform extract was passed through a 20×1-cm alumina column with chloroform as the eluent, collecting the fraction with R_f 0.4. Evaporation of the solvent gave 0.024 g (22%) **8** as gray crystals; mp 138-140°C (octane). The aqueous solution containing 3-aminoindazole hydrochloride was treated with conc. aqueous ammonia to pH 7-8. The precipitate formed was filtered off to give 0.033 g (50%) 3-aminoindazole **5a** as gray prisms; mp 153-154°C (benzene).

1-Benzylamino-3-nitroindazole (9). A sample of sodium borohydride (0.15 g, 3.9 mmol) was added in portions to a solution of 1-benzylideneamino-3-nitroindazole **7** (1 g, 3.8 mmol) in 2-propanol (460 ml) and left for 24 h at room temperature. Four fifths of the solvent was distilled off. The residue was diluted with water (100 ml) and neutralized with concentrated hydrochloric acid to pH 7. The reaction mixture was extracted with two 5-ml chloroform portions and passed through a 30×2.5-cm alumina column with chloroform as the eluent, collecting the fraction with R_f 0.9. Evaporation of chloroform gave 0.2 g (20%) **9** as yellow crystals; mp 118°C (octane). IR spectrum, ν, cm^{-1}: 1389, 1520 (NO_2), 1620 (ring), 3280 (NH). ^1H NMR spectrum, δ, ppm, *J* (Hz): 4.50 (2H, d, CH_2, ^3J = 5.03); 5.55 (1H, t, NH, ^3J = 5.02); 7.30 (4H, m, 2'-H, 6'-H); 7.40 (3H, m, 5-H, 7-H); 8.18 (1H, m, 4-H). Found, %: C 62.92; H 4.77; N 21.18. $C_{14}H_{12}N_4O_2$. Calculated, %: C 62.68; H 4.50; N 20.88.

3-Amino-1-benzylindazole (11). A sample of 3-aminoindazole **5a** (0.133 g, 1 mmol) was added to a solution of KOH (0.14 g, 2.5 mmol) in DMSO (20 ml), stirred for 5 min, and, then, benzyl chloride (0.144 ml, 1.25 mmol) was added in a single portion. The mixture was stirred for 2 h at room temperature and diluted with water (30 ml). The emulsion obtained was extracted with three 10-ml chloroform portions. The chloroform extract was washed with two 10-ml water portions and passed through a 20×1.5-cm alumina column with chloroform as the eluent, collecting the fraction with R_f 0.6. Evaporation of chloroform gave 0.158 g (70%) **11** as cream-colored plates; mp 115-116°C (octane) (116°C (ethanol) [10]). ^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 3.75 (2H, br. s, disappears after deuteration, NH_2); 5.35 (2H, s, CH_2); 7.01 (1H, m, 5-H); 7.24 (7H, m, 2'-H, 6'-H, 6-H, 7-H); 7.53 (1H, m, 4-H).

4-Aminobenzo-1,2,3-triazine (12). A. A solution of 1,3-diaminoindazole **1g** (0.1 g, 0.67 mmol) in chloroform (20 ml) was left for 30 days at room temperature. A brown precipitate gradually settled from the solution, which was filtered and washed with chloroform to give 0.032 g (33%) **12** as brown crystals; mp 270°C (266°C [11]). IR spectrum, ν, cm^{-1}: 1655 (C=N), 3151, 3399 (NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.00 (1H, m, 6-H); 8.15 (2H, m, 7-H, 8-H); 8.50 (1H, m, 5-H); 9.10 (br. s, NH_2, disappears after deuteration).

B. A solution of 3-azido-1-aminoindazole **1h** (0.1 g, 0.57 mmol) in chloroform (20 ml) was left for 27 days at room temperature. A brown precipitate gradually settled from the solution, which was filtered off and washed with chloroform to give 0.02 g (24%) **12** as brown crystals; mp 270°C.

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